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Histogenesis of Coronary Arteriosclerosis

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The coronary arteries of 250 individuals dying suddenly from traumatic or natural causes were studied. Many different histopathologic processes were found to participate in the development of coronary arteriosclerosis. The earliest changes which occurred, even in infants, were increased fibroblastic activity, deposits of mucopolysaccharide and degeneration of elastic tissue. These changes were not related to lipid deposition. Moderately advanced lesions were characterized by regeneration of elastic tissue, formation of collagen and lipid deposition. The far-advanced lesions showed hyalinization, abundant lipid deposition, calcification, intramural hemorrhage and thrombosis. The possible mechanisms involved in the development of coronary arteriosclerosis are discussed.

THE PURPOSE of this study, initiated several years ago, was to determine the sequence of histologic changes in the development of coronary arteriosclerosis in man. As a result of this study it has become apparent to us that multiple histologic processes participate in the development of coronary arteriosclerosis. These processes have a definite sequence in their appearance. The primary or earliest changes have already developed in most individuals by the second decade and in all individuals by the third decade.

MATERIALS AND METHODS

The data for this study were obtained from autopsies on 250 individuals, nearly all of whom died suddenly without a preceding debilitating illness. The ages of these individuals ranged from 4 months to 90 years.

The hearts were weighed to the nearest gram. The major coronary arteries were sectioned at intervals of 0.3 to 0.4 cm. and multiple blocks of tissue were removed for histologic study from the left anterior, the left circumflex and the right coronary arteries from the proximal segments in areas of maximum sclerotic thickening. Sections of myocardium, endocardium and small coronary arteries were taken. The pieces of tissue were fixed in formalin and embedded in paraffin or carbowax. Multiple sections 7 microns thick were taken from the paraffin blocks and stained with hematoxylin and eosin. Contiguous sections of coronary arteries were stained for elastic tissue and frequently for mucoid ground substance.[1] In 120 cases contiguous sections of the coronary arteries embedded in carbowax were stained for both lipid[2] and mucopolysaccharide. (Both toluidin blue and colloidal iron technics for mucopolysaccharide were used in many cases.) An unstained section processed in carbowax was used for examination under crossed polarizing lenses.

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OBSERVATIONS

A general survey of the material indicated that there were multiple pathologic processes occurring in coronary arteriosclerosis. These processes were: (1) subendothelial fibroblastic proliferation of the intima; (2) appearance of increased amounts of mucoid ground substance in the intima and occasionally in the media; (3) fragmentation and degeneration of elastic tissue; (4) formation of collagen fibers in the intimal plaques; (5) regeneration of elastic tissue; (6) deposition of lipid and cholesterol; (7) "hyaline degeneration" of fibrous connective tissue; (8) deposition of calcium; (9) intramural hemorrhage and thrombosis.

Although there was marked individual variation there was a greater degree of sclerosis

in the older age groups (fig. 1). The sclerotic changes were less severe in the smaller arteries. These findings were essentially similar to those reported by White and his co-workers.[3]

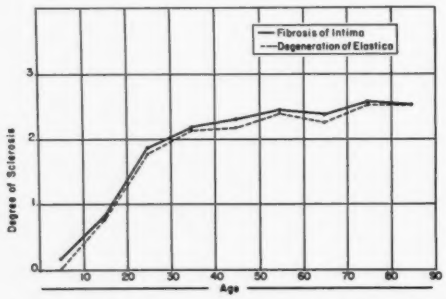


FIG. 1. The average degrees of fibrosis of the intima and degeneration of the internal elastic membrane in the proximal segments of the coronary arteries by decades.

Nonsclerotic Coronary Arteries. Completely nonsclerotic major coronary arteries were not present except in very young individuals. The intima consisted of an endothelial layer beneath which were occasional fibroblasts (fig. 2*A*). In cross sections of arteries the internal elastic membrane was a delicate wavy layer. In longitudinal sections this layer appeared as a slender band separating the intima from the media. Thus, this layer was essentially a continuous tube (except for the ostia of branches) with longitudinal corrugations. A few delicate elastic fibrillae were present in the medial coat of smooth muscle. Mucoid ground substance was present in small amounts in the media. The adventitia consisted of a small amount of collagenous connective tissue and a few delicate elastic tissue fibrillae.

Early Coronary Arteriosclerosis. The early changes were present frequently even in apparently healthy young individuals in the first or second decade of life, who died suddenly of traumatic injuries and could be consistently demonstrated in the proximal segments of the coronary arteries of all individuals after the second decade.

The early lesions, which were best demonstrated in the coronary arteries of young individuals, were characterized by a slight diffuse increase in thickness of the intima. Occasionally this process was localized and involved only a small part of the circumference. Several histologic changes seemed to occur simultaneously. These were: (1) appearance of increased amounts of mucoid ground substance in the intima and media; (2) proliferation of

FIG. 2.*A*. Nonsclerotic coronary artery; age 1 year 3 months; Weigert elastic tissue stain. × 275.

B. Early coronary arteriosclerosis; age 4 months; Verhoeff elastic tissue stain. The intima shows fibrous thickening; degeneration and regeneration of the internal elastic membrane are present. × 150.

C. Early coronary arteriosclerosis; age 56 years. Colloidal iron impregnation. The intima shows a mild diffuse thickening and increased mucopolysaccharide. The media shows deposits of mucopolysaccharide. × 12.5.

D. Early coronary arteriosclerosis; age 16 years. Colloidal iron impregnation. There is diffuse thickening of the intima. × 150.

E. Early sclerosis of coronary artery; age 24 years. Sudan III and hematoxylin. There is diffuse fibrosis of the intima. The lower segment of the thickened intima is filled with lipid; the upper segment contains none. × 12.5.

F. Moderate advanced coronary arteriosclerosis; age 50 years. Colloidal iron impregnation. Large amounts of mucopolysaccharide are present in the intima and are greatest along the advancing intimal border of the fibrous plaque. There is some collagenization at the base of the plaque. × 150.

G. Early coronary arteriosclerosis; age 35 years. Verhoeff elastic tissue. Several layers of fragmented elastic tissue appear in the intima adjacent to the media. The part of the intima closest to the lumen shows no elastic fibers and contains increased amounts of mucopolysaccharide. There is an increased amount of elastic tissue in the media.

H. Far advanced coronary sclerosis; age 43 years. Colloidal iron impregnation. Small deposits of mucoid ground substance are present in some "hyalinized" areas of the plaque in the large artery. Vacuoles due to lipid are present at the base and in the center of this plaque. Small areas of calcification (pale blue) are present. A branch of this artery at the right shows moderately advanced sclerosis; large amounts of mucopolysaccharides are present in the intima. × 150.

(*The use of color in this illustration is made possible by a grant from Winthrop-Stearns, Inc., to the publication fund of the American Heart Association.*)

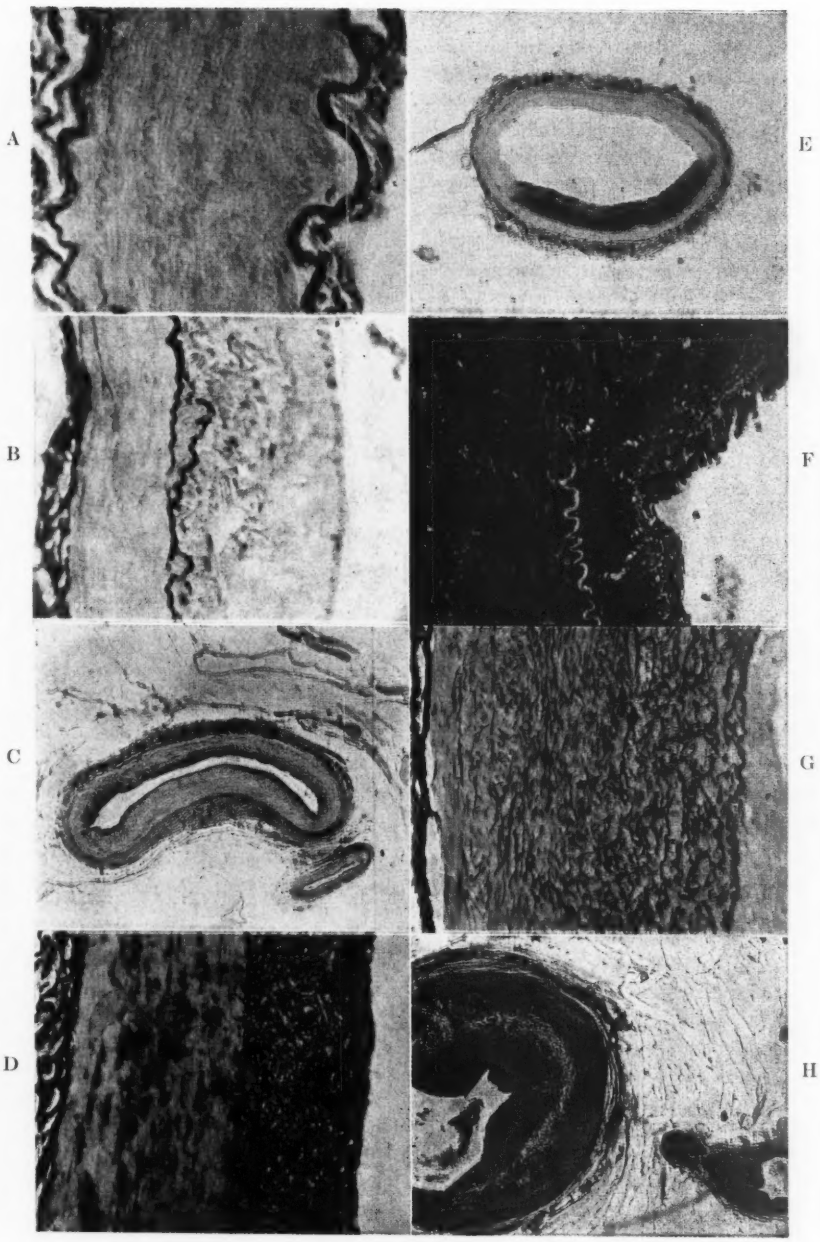


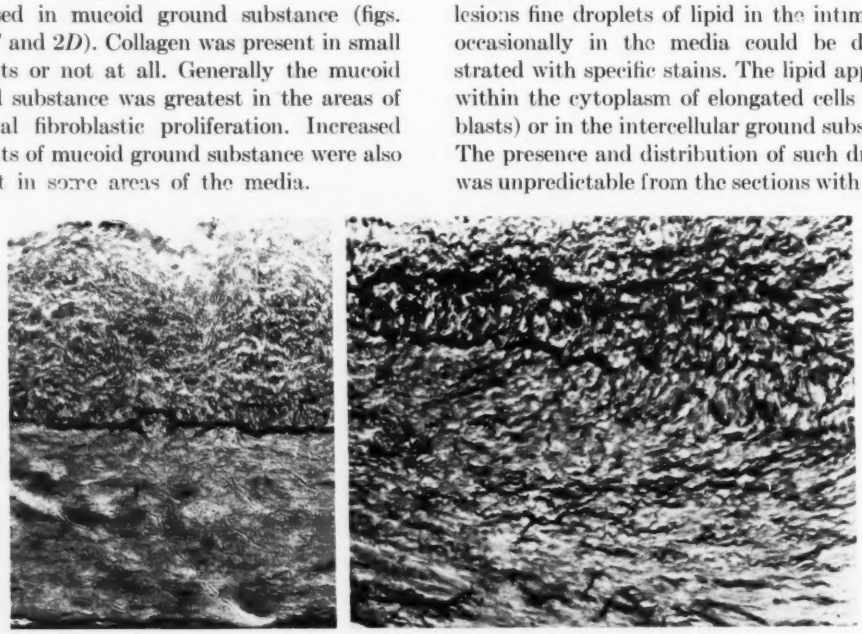
FIG. 2. Legend on facing page.

subendothelial fibroblasts; and (3) small areas of degeneration of the internal elastic membrane.

Fibroblastic proliferation of the intima was seen in all individuals past the age of 20. In most of the early lesions the fibroblasts were dispersed in mucoid ground substance (figs. 2*B*, 2*C* and 2*D*). Collagen was present in small amounts or not at all. Generally the mucoid ground substance was greatest in the areas of maximal fibroblastic proliferation. Increased amounts of mucoid ground substance were also present in some areas of the media.

tic membrane was completely reestablished in some of these areas.

No direct or consistent relationship of lipid to the early lesions could be demonstrated. In arteries showing early sclerosis, lipid was frequently absent. In other arteries with early lesions fine droplets of lipid in the intima and occasionally in the media could be demonstrated with specific stains. The lipid appeared within the cytoplasm of elongated cells (fibroblasts) or in the intercellular ground substance. The presence and distribution of such droplets was unpredictable from the sections with hema-



A B

FIG. 3.*A*. Early coronary arteriosclerosis; age 16 years. Verhoeff elastic tissue stain. A short segment of ruptured internal elastic membrane is being carried in by herniation of the media. × 150.

B. Early coronary arteriosclerosis; age 16 years. Verhoeff elastic tissue stain. The internal elastic membrane shows small areas of rupture and reduplication at the left where sclerosis is slight. At the base of a fibrous plaque to the right the elastic tissue is almost completely disrupted. Increased amounts of elastic tissue appear in the media. × 150.

Concomitant with the increase in mucoid ground substance and fibroblastic proliferation there were focal areas of degeneration of the internal elastic membrane. These areas of degeneration were most commonly seen beneath fibrous plaques. In some instances segments of degenerating internal elastic membrane were carried inward by herniations of smooth muscle (fig. 3*A*). There was subsequent fibrous replacement of the smooth muscle. In some areas there were successive layers of degenerating and regenerating elastic tissue (fig. 2*B*). The continuity of the internal elas-

toxylin and eosin, elastic tissue or colloidal iron stains. Lipid droplets, when present, were in the thickened intima, media or in both layers. In some arteries showing early fibrotic intimal changes and lipid deposition, the fat was present only in some segments of the thickened intima and not necessarily related to a fibrous plaque (fig. 2*E*). Macrophages containing lipid were almost never observed in any of the early lesions.

Moderately Advanced Coronary Arteriosclerosis. With progression of the arteriosclerotic process, fibrous plaques, as well as a greater

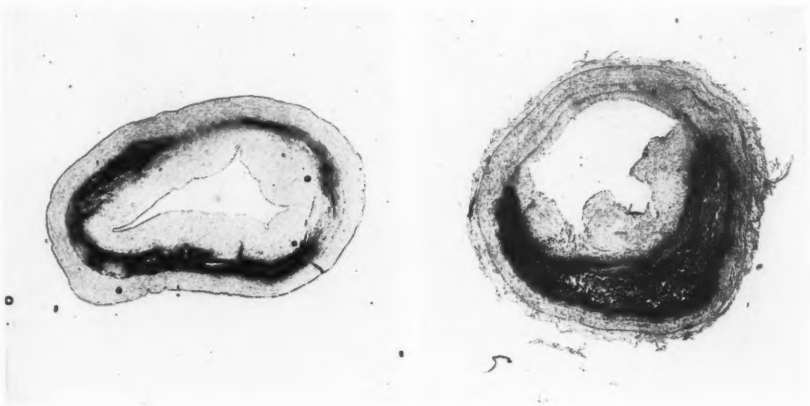
degree of diffuse fibrous thickening of the intima, were consistently present. The base and centers of the plaques contained moderate amounts of collagen; the advancing intimal borders of the plaques were composed of loosely arranged fibroblasts and mucoid ground substance quite similar in appearance to the early lesions (fig. 2*F*). Mucopolysaccharide was more evident in the developing plaques than elsewhere; however, this was not a universal finding.

The internal elastic membrane showed more fragmentation and reduplication than in the early lesions (figs. 2*G* and 3*B*). The continuity of this membrane had been re-established in some areas of previous rupture.

Lipid was always present and appeared as both fine and coarse droplets. The distribution of the lipid was noteworthy in that the lipid was almost always greatest at the bases or in the centers of the plaque and least along the endothelial border (figs. 4*A*, 4*B*). The media showed more mucoid ground substance and greater collagenization than in most of the early lesions. Beginning encroachment of intimal plaques on the media was also noted.

Far Advanced Coronary Arteriosclerosis. Far advanced lesions presented changes not encountered in the earlier stages. Hyaline changes and calcification became apparent at this stage of development. The bases and centers of intimal plaques were hyalinized, and in these areas the lipid content (including crystalline cholesterol) was greatest. The hyaline material frequently was positive for mucopolysaccharide although the staining reaction was not as intense (fig. 2*H*). Lipid was often present in large globules; lipid-filled macrophages were encountered frequently. The advancing intimal borders of hyalinized plaques were cellular and contained little or no lipid; these areas resembled the early lesions. Calcification first became apparent at the junction of the thickened intima and media (frequently along the internal elastic membrane). Some areas of hyalinized plaques also were calcified. The elastic tissue was markedly degenerated and occasionally completely gone. Lymphocytic infiltration of the adventitia was a frequent finding.

Severe stenosis of the lumina or thrombosis occurred in arteries showing far advanced



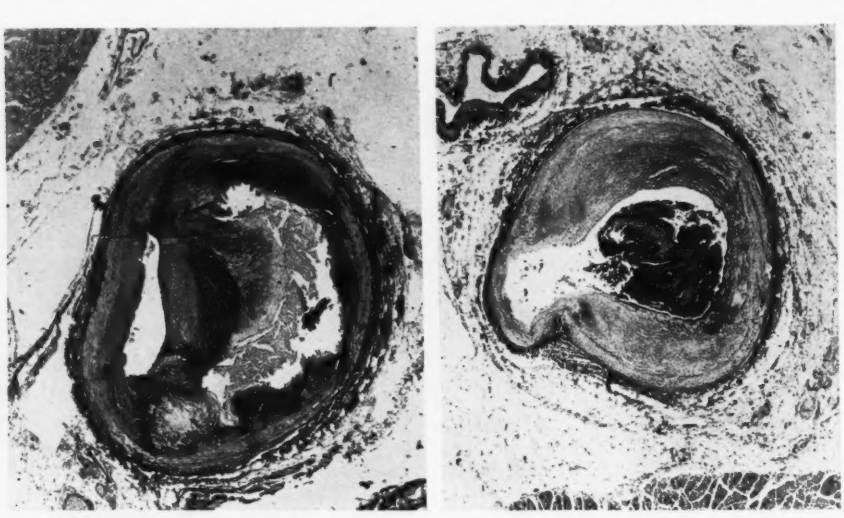
A B

FIG. 4.*A*. Moderately advanced coronary arteriosclerosis; age 49 years. Sudan III and hematoxylin. Lipid is present in large amounts at the base of the thickened intima adjacent to the media, whereas the advancing edges of fibrous tissue contain no lipid. × 12.5.

B. Far advanced coronary sclerosis; age 31 years. Sudan III and hematoxylin. A large amount of lipid is present at the base of the plaque. There is little or no lipid in either the endothelial border of the plaque or in the portion of slightly thickened intima opposite the plaque. × 12.5.

changes (figs. 5*A* and 5*B*). In some of the hyalinized and fatty plaques there were focal to large areas containing hemosiderin and lipid-laden macrophages as well as lymphocytes. In considerable numbers of thrombosed arteries, hemorrhage into an intimal plaque had occurred with extrusion of hemorrhagic material, hyalinized and calcified tissue and lipid into the lumen.

In some individuals showing advanced thickening and hyalinization of the intima, the coronary arteries were not stenotic but had dilated lumens. These were encountered more frequently in the 70 to 90 year old group.



A B

FIG. 5.*A*. Far advanced coronary arteriosclerosis; age 75. Verhoeff elastic tissue stain. There is complete loss of elastic tissue at the base of the large plaque. In the center and at the base of the plaque there are acicular clefts and vacuoles due to lipid. Calcification is present at the base of the plaque. × 12.5.

B. Far advanced coronary arteriosclerosis with thrombosis; age 69. Verhoeff elastic tissue stain. × 12.5.

DISCUSSION

There is a remarkably close association of fibroblastic proliferation, increased amounts of mucoid ground substance and degeneration of elastic tissue in the earliest sclerotic changes of coronary arteries. These findings are essentially similar to the careful observations of earlier workers, notably Virchow,[4] Aschoff,[5] Schultz,[6] and Wolkoff.[7] The second stage is characterized by maturation of the "scar" (deposition of collagen) and regeneration of elastic tissue from the mucoid substrate. The third stage is one of degeneration or senescence characterized by the appearance of large amounts of lipid, hyalinization of connective tissue fibrillae and calcification. The affinity of hyaline material for colloid iron suggests that this material is related to the mucoid ground substance of the earlier lesions. It would seem likely that hyaline material represents an abnormal polymer of mucoid ground substance and reflects the process of aging. Such a degenerative change may well be expected to predispose toward intramural hemorrhage and thrombosis. The final stage of intramural hemorrhage and thrombosis is regarded as the result of degeneration of connective tissue ground substance and collagen and stenosis of the lumens of the involved arteries. The above histogenetic sequence is undoubtedly modified by many local and systemic factors.

The remarkable frequency with which fibro-

sis of the intima, increased mucoid ground substance and fragmentation of the internal elastic membrane occurs even in young individuals logically raises the question as to whether or not these changes may be regarded as "normal" or nonpathologic. Although we do not intend to discuss this question at present it should be pointed out that processes which predispose to or cause eventual dysfunction of an organ should by definition be regarded as pathologic.

The lack of correlation between lipid and early arteriosclerotic changes leads us to believe that the deposition of lipid is not the initiating factor in the development of coronary arteriosclerosis. Dock[8] and Moschcowitz[9] have more recently pointed out that intimal fibrosis and lipid deposition are separate pathologic entities. Wilens[10] likewise observed fibrous plaques with little or no lipid in the aorta; however, he suggests that these plaques may be related to previous lipid deposition in infancy. While it is true that individuals with certain derangements in lipid metabolism may develop severe coronary arteriosclerosis and equally true that experimentally induced hypercholesterolemia may evoke profound "cholesterol arteriosclerosis," the histogenesis of such lesions bears little resemblance to histogenesis of coronary arteriosclerosis of the type that is commonly encountered in man. Indeed, if alterations in lipid metabolism play a role in the development of coronary arteriosclerosis, such derangements are localized to preexisting fibrous plaques. A possible mechanism for deposition of cholesterol in areas rich in mucoid ground substance has recently been suggested by Faber.[11]

On the other hand, in the moderately advanced and far advanced lesions of coronary arteriosclerosis, lipids, including cholesterol are consistently present. This may be the result of one or more of the following factors: (1) increased affinity of an abnormal intercellular ground substance for lipids; (2) abnormal lipid metabolism localized to focal areas; (3) liberation of lipids as a result of cellular degeneration; (4) a superimposed systemic defect in lipid metabolism which is manifested by deposition of lipid only in areas of preexisting damage. The distribution of lipid was noteworthy in that the largest amounts as well as the earliest appearance were generally in the central areas or at the bases of sclerotic plaques. This indicates that the vasa vasorum are more likely the source of any exogenous lipid in sclerotic plaques than the transintimal imbibition of lipid from the lumen of the vessel. Transintimal migration of lipid-laden macrophages was practically never observed in early lesions.

Fragmentation of the internal elastic membrane as a result of intra-arterial tension greater than the tensile strength of elastic tissue must be considered as a possible initiating mechanism in coronary arteriosclerosis. It is likely that the maintenance of elastic tissue and collagen by metabolic processes mediated through the intercellular ground substance are involved in the process of arteriosclerosis. Alterations in this mechanism secondary to nutritional or hormonal imbalance would produce quantitative or qualitative changes in intercellular ground substance, collagen and elastic tissue. The similarity between the arteriosclerotic lesions of monkeys in experimental pyridoxine deficiency and the early lesions of coronary arteriosclerosis found in man has been mentioned in a previous publication from this laboratory.[12] Although the significance of pyridoxine deficiency in human arteriosclerosis is not known, its role through the enzyme systems concerned with protein metabolism and thus involved in the normal maintenance of connective tissue and ground substance bears further investigation.

All of the various histogenetic changes from early to late may occur not only in the same individual but are frequently observed in the same plaque. The earliest changes are always observed on the endothelial side of the plaque, superimposed on the layers with moderately advanced and late changes.

Conclusions

A study of the major coronary arteries of 250 individuals, most of whom died suddenly from traumatic or natural causes, indicates that multiple pathologic processes participate in the development of coronary arteriosclero-

sis and have an orderly sequence in their development. These processes bear certain similarities to the formation of scar tissue.

The earliest sclerotic lesion is characterized by the apparently simultaneous appearance of proliferation of subendothelial fibroblasts, increased amounts of mucoid ground substance and fragmentation of the internal elastic membrane. No relationship between these changes and the occasional presence of fine droplets of lipid could be demonstrated. The moderately advanced and far advanced lesions differed from the early lesions in that lipid was always present. In these lesions there was greater fibrosis of the intima and degeneration of the internal elastic membrane. The earlier stages of fibroblastic proliferation and increased mucoid ground substance, when superimposed on the later stages, were always present on the endothelial side of the plaque. "Hyaline" degeneration of the fibrous tissue and calcification occurred in the far advanced lesions. The possibility of "hyaline" degeneration resulting from abnormal polymerization of mucoid ground substance is suggested.

Acknowledgments

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A Comparative Evaluation of Tromexan and Dicumarol in the Treatment of Thromboembolic Conditions—Based on Experience with 514 Patients

A Report of the Committee on Anticoagulants of the American Heart Association

By Louis A. Scarrone, M.D., Dorothy Fahs Beck, Ph.D., and Irving S. Wright, M.D.

An evaluation of the comparative actions of Tromexan and dicumarol is herein reported. Five hundred fourteen patients were studied; a total experience of 6,642 days of Tromexan therapy and 5,006 days of dicumarol therapy were reviewed and analyzed. Previous reports of the more rapid initial prolongation of the prothrombin times and more rapid return to normal following cessation of therapy with Tromexan were confirmed. During adequate therapy the protection against thromboembolism was approximately equal for the two drugs. In other respects and with minor variations Tromexan and dicumarol were found to be quite comparable. The general advantages of anticoagulant therapy in the prevention of deaths and thromboembolic complications in myocardial infarction were comfirmed.

FOLLOWING the demonstration that anticoagulant therapy is of value in the treatment of a variety of thromboembolic disorders, investigators have sought to find more satisfactory agents than heparin and dicumarol. Paritol,[1] phenylindanedione,[2] BL-5,[3] Tromexan[4] and, recently, Treburon[5] have been tested for clinical use. The reports in the literature regarding Tromexan appeared to justify a more comprehensive clinical trial of this drug.

The Committee on Anticoagulants of the American Heart Association has attempted to evaluate the merits of Tromexan* as compared with dicumarol, now in common use.† An attempt has been made to answer certain questions regarding: (1) the relative speeds of onset and cessation of action; (2) the toxicity of Tromexan, exclusive of hemorrhage, if any; (3) the comparative hemorrhagic tendencies of the two drugs; (4) the relative ease of handling the drugs, and (5) their relative clinical effectiveness.

With a view to accumulating data on these questions, the Committee initiated a study of the two drugs among the participating hospitals listed in table 1. Patients with a variety of thromboembolic disorders were treated in this series. Details of each individual case history were compiled on extensive master forms and reviewed by us. A total of 514 cases was accumulated in approximately a 12 month period and forms the basis of this report.

Historical Review of Tromexan

Tromexan is a coumarin derivative, 3,3′-carboxymethylenebis (4-hydroxycoumarin) ethyl ester (also referred to as Pelentan, BOEA and DEA). The acid form was prepared in 1940,[6] but was relatively inactive. Esterification[7] caused a marked rise in activity, and this form was extensively investigated by a number of European workers. The lethal dose for animals (mice and rabbits) was reported as approxi-

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* Known as Peletan in Czechoslovakia. Tromexan is sometimes referred to as DEA, from an alternate name, 4,4′-dihydroxydicumarinyl ethyl acetate. The Tromexan was supplied through the courtesy of Geigy Pharmaceuticals.

† The previous Committee on Anticoagulants of this Association has reported on the use of dicumarol in myocardial infarction.[17] As more than 1000 patients were studied in that series, frequent references are made in this study to the results compiled in the previous work.

mately four to five times that of dicumarol.[8] Reinis and Kubik[9] gave human requirements as approximately four times that of dicumarol and stated maximum diminutions in prothrombin occurred within 24 hours, with recovery in 48 hours. Degradation products labeled Tromexan A and B were recovered from the urine of humans and animals and found to be relatively inactive.[10] Rapid action and reversibility in contrast to dicumarol were attested in numerous reports.[8, 9, 11, 12, 13]

In the United States, Burke and Wright,[14] Solomon,[15] and Barker[16] have reported clinical experiences with this drug. In the Burke and Wright report 112 patients with various thromboembolic diseases were treated. Their data indicated that following a single dose of from 1200 to 1800 mg. the prothrombin time frequently showed an increase within 18 to 24 hours, rose to therapeutic levels in an average of 30 hours, and fell to normal levels between 48 and 60 hours. The dose required for this response varied with different individuals. Maintenance dosages averaged 600 to 900 mg. per day, either in a single dose or in divided daily doses. On the basis of these figures and further experience with Tromexan at The New York Hospital, an initial dose of 1500 or 1800 mg. was recommended to the participating hospitals (in the absence of contraindications), with subsequent doses to be determined by the daily prothrombin level.*

Study Plan and Composition of the Sample†

The case records for the study were collected on a cooperative basis under which seven different hospitals pooled their experience. Of the records submitted, 514 met the criteria for acceptance for the study.‡ These were distributed by hospitals as follows: 47 from Bellevue Hospital in New York City, 119 from Henry Ford Hospital in Detroit, 22 from Jackson Memorial Hospital in Miami, 115 from Lakeside Hospital in Cleveland, 28 from the Mayo Clinic in Rochester, 100 from The New

Table 1.—*The Committee on Anticoagulants of the American Heart Association, Participating Hospitals and Responsible Investigators**

Hospitals	*Investigators*
Bellevue Hospital, *New York*	E. Hugh Luckey, M.D.
Henry Ford Hospital, *Detroit*	F. Janney Smith, M.D.
Jackson Memorial Hospital, *Miami*	E. Sterling Nichol, M.D.
Lakeside Hospital, *Cleveland*	Harold Feil, M.D.
Mayo Clinic, *Rochester*	Nelson W. Barker, M.D.
Pennsylvania Hospital, *Philadelphia*	Joseph B. Vander Veer, M.D.
The New York Hospital, *New York*	Irving S. Wright, M.D.

Consultants
Ralph S. Overman, Ph.D.
Grafton E. Burke, M.D.

Central Laboratory
Irving S. Wright, M.D., *Chairman of Study*
Louis A. Scarrone, M.D., *Coordinator*
Dorothy F. Beck, Ph.D., *Statistician*

* Appreciation is expressed to the residents and fellows of the various participating hospitals who have contributed their efforts towards this report, to Jane F. Jackson, M.A., for assistance with the statistical analysis, to Jean Newbauer for typing the manuscript and to the New York Heart Association for the use of its facilities.

* Daily dosage requirements average 450 mg. to 900 mg. Some patients require only 300 mg. per day, others as much as 1200 mg. The widest range in this study was 150 mg. every other day and 1650 mg. per day.

† To reduce the length of the report, most of the statistical tables have been omitted. A supplementary set of these supporting tables in mimeographed form will be furnished on request.

‡ The sample omitted patients dying within 24 hours of hospitalization and cases treated with anticoagulants because of an error in diagnosis, provided the revised diagnosis involved no risk of thromboembolism sufficient to justify such therapy.

York Hospital in New York City,* and 83 from Pennsylvania Hospital in Philadelphia. Most of the hospitals included private patients as well as ward cases in their samples, but ward cases predominated in the total.

A variety of thromboembolic diagnoses were included in the sample and no attempt was made to regulate the proportion of the total sample in each diagnostic group. For the duration of the study the cooperating hospitals undertook to treat with either Tromexan or dicumarol each patient admitted to a cooperating service and diagnosed as having a thromboembolic condition except when specific medical contraindications to the use of anticoagulants were present. Additional cases were also treated with these anticoagulants for prophylactic purposes at the discretion of the cooperating staff. Two hundred and sixty-two, or 51 per cent of the cases thus collected, were patients with myocardial infarction; 87, or 17 per cent, were patients with thrombophlebitis or venous thrombosis; 41, or 8 per cent, were patients with pulmonary infarction (or pulmonary infarction combined with thrombophlebitis or venous thrombosis); 20, or 4 per cent, were patients with other arterial thrombosis or embolism (cerebral, renal, and others), and 104, or 20 per cent, were patients receiving anticoagulants as a protection against possible thromboembolic developments in coronary insufficiency,* postoperative states, auricular fibrillation with rheumatic heart disease, or miscellaneous conditions. The number of patients in each of these groups receiving each anticoagulant is given in table 2. The period of therapy was determined by the attending physician in each case, but records for a six-week period were requested in the instance of patients with myocardial infarction where feasible. Records beyond 42 days were not tabulated unless the patient continued in the hospital for a longer period and then only for a maximum of 92 days.

To assure nonselectivity, the hospitals were urged to use Tromexan in the treatment of patients admitted on the even days of the month and dicumarol for those admitted on odd days, or vice versa. All the cooperating hospitals except the Mayo Clinic (other programs interfered) attempted to follow this recommended procedure. Administrative errors, delays in instructions, and other difficulties prevented the plan from working out perfectly, with the result that a number of exceptions were made in the anticoagulant to which pa-

TABLE 2.—*Number of Patients Studied and Number of Deaths, by Diagnosis and Anticoagulant Received*

Diagnostic Group	Number of Patients in Sample				Number of Deaths			
	Total	Anticoagulant Used			Total	Anticoagulant Used		
		Tromexan	Dicumarol	Both Tromexan and Dicumarol		Tromexan	Dicumarol	Both Tromexan and Dicumarol
Myocardial infarction	262	139	106	17	31	15	16*	—
Thrombophlebitis or venous thrombosis	87	54	18	15	2	1	—	—
Pulmonary infarction†	41	22	17	2	4	3	1	—
Other arterial thrombosis or embolism	20	10	9	1	3	1	1	1
Coronary insufficiency and prophylactic purposes	104	63	31	10	4	4	—	—
Total sample	514	288	181	45	44	24	18	2

* Including two deaths in which Paritol may have contributed to death.
† With or without accompanying thrombophlebitis or venous thrombosis.

* Five cases treated by staff members of The New York Hospital at Doctors Hospital are included in this total.

* Patients originally diagnosed as probably having myocardial infarction but found later to have coronary artery disease but no infarction were included here.

tients were assigned.* When assembled, the alternate series was found to consist of 355 cases, of which 160 had been treated with dicumarol, 172 with Tromexan, and 23 with both drugs.† Fortunately, the exceptions were made in both directions and there appeared to be no systematic basis for the shifts made except that dicumarol was selected by some physicians when long-term home therapy was contemplated. Some of the patients in the mixed drug group had been switched to dicumarol in preparation for ambulatory treatment. In other instances one anticoagulant did not give satisfactory results with a particular patient so that the other was tried. The choice of one drug in preference to the other did not appear to be associated with observable characteristics of the patients in any way that would affect the comparability of the two groups.

Since it was desirable that a larger number of cases be studied than this alternate-day procedure had procured, these cases were supplemented with 159 cases, most of which had been treated with Tromexan,‡ collected under circumstances where there had been no systematic alternation with dicumarol. These additions brought the total cases available for analysis to 514, of which 181 were dicumarol cases, 288 Tromexan cases, and 45 mixed drug cases. These cases received a total of 6,642 days of therapy with Tromexan only and 5,006 days with dicumarol only.§

In view of these additions and exceptions, confidence in the comparability of the two groups must rest primarily on an analysis of the types of cases included rather than on the presumed randomness of the alternation procedure. The most conspicuous difference between the dicumarol and Tromexan group is that the latter included a higher proportion of cases having a diagnosis of thrombophlebitis.* When this diagnosis is omitted, the distribution of the two groups by diagnosis is similar. The excess of thrombophlebitis cases in the Tromexan group was produced by the concentration in this category of these "special" Tromexan cases (cases collected without alternation with dicumarol). Correction of the basic complication and hemorrhage rates for this difference in sampling was attempted and is reported in subsequent sections.

The Tromexan and dicumarol groups also differed with respect to the proportion of the total days of anticoagulant therapy observed that fell in the early period of the illness, particularly in the first two weeks.† The corrected basic rates previously mentioned also correct for this dissimilarity between the two groups, which is again due to the "special" Tromexan cases added to increase the sample since they happened to have particularly short periods of therapy. This same difference is reflected also in the total periods of therapy. The Tromexan group received an average of 21 days of protection with Tromexan only, that is, days without supplementation with heparin or Paritol, and the dicumarol group, 24 days with dicumarol only. Tromexan cases were observed for a total of 34 days on the average and dicumarol cases for an average of 37 days.

A third difference occurred in a minor degree with respect to supplementation with other anticoagulants, a procedure permitted at the discretion of the attending physicians. Supplementation with heparin was the same in the two groups, 21 per cent of the cases in each group receiving supplementation with heparin for an average of slightly less than three days for each case with supplementation. However, 17 per cent of the dicumarol group and only 8 per cent of the Tromexan group received Paritol, for averages of three and two days re-

* Twenty-eight per cent of the patients that should have received dicumarol received Tromexan only or both anticoagulants and 19 per cent of those that should have received Tromexan received dicumarol only or both drugs.

† Patients from one cooperating service that attempted alternation unsuccessfully are included among group referred to as "special."

‡ Of these, 116 received Tromexan only; 21, dicumarol only; and 22, both Tromexan and dicumarol.

§ When a case received both drugs, the days were divided between the two anticoagulants according to the actual days each was received.

* Nine per cent of the dicumarol days and 16 per cent of the Tromexan days were observed in thrombophlebitis or venous thrombosis cases.

† Thirty-eight per cent of the Tromexan days fell in the first two weeks of the illnesses studied and 38 per cent in the third and fourth weeks, whereas the corresponding percentages for dicumarol therapy were 34 and 36 respectively.

spectively. Comparisons between the drugs are protected from the influence of this extraneous factor by the use of day rates that exclude all periods of supplementation.

On the test of severity of onset of the illness the samples favor Tromexan slightly, for 23 per cent of the dicumarol cases as compared with 18 per cent of the Tromexan cases were considered severe at onset by the reporting physician.* The difference is due again to the addition of the "special" Tromexan cases, an unduly large number of which were mild at onset. Since a precise definition of "severe at onset" is difficult and the difference is small, corrections for this factor were not attempted. If corrections had been made, they might have increased slightly the thromboembolic complication rate for Tromexan.

Because of the small numbers in some diagnostic subgroups, corrections for age and sex differences also were not feasible. Fortunately, differences in age were slight. Forty-six per cent of the Tromexan cases were 60 years of age or older but only 38 per cent of the dicumarol cases; however, the age averages for the two groups were closely similar, 56 years and 55 years respectively. Since no clearly significant relationship between age and complications and hemorrhages was found in the dicumarol study,[17] it may be assumed that these differences do not affect the comparisons between the two anticoagulants. In sex composition the two groups could hardly have been more closely similar, for 65 per cent of each were males and 35 per cent females. Not all diagnostic subgroups were thus alike in age and sex composition and other characteristics compared, but in general the larger and more homogeneous groups showed reasonable similarity.†

Analysis of the previous medical history of the two groups, particularly with respect to the presence of previous episodes of bleeding or thromboembolic episodes, was not feasible within the time limits, but the intensive review of the records involved in the complication and hemorrhage analysis did not leave the impression that any obvious selection or bias occurred in this respect and there is no logical reason to expect selection.

In general, it may be concluded that while differences between the two samples did occur with respect to diagnosis, period of therapy, and severity, these differences cannot be considered the explanation for the differences between the two drugs reported, for corrections have been made for two of the three differences and the third is such as would probably increase slightly rather than reduce the reported differences. Where conclusions are believed affected by sampling differences, qualifying statements have been appended.

Prothrombin Time Reporting

Local differences in technics for performing prothrombin time tests constitute another possible source of error in comparisons between two anticoagulants when the basic data are obtained from more than one hospital. To overcome this difficulty, in so far as possible, the percentages of prothrombin activity approximately equivalent to all prothrombin times reported in seconds by the cooperating hospitals were first determined on the basis of dilution curves for normal blood submitted by the hospitals concerned. These percentages were then converted back into seconds, this time with a standardized meaning, by means of the composite prothrombin time curve developed for purposes of the dicumarol study.* Table 3, developed for use in this conversion procedure, indicates the standardized meanings (in terms of percentages of prothrombin activity) of 17, 25 to 39, 50 to 59 and 60 seconds or more as used in the text.

This table illustrates dramatically the great divergencies in the meaning of prothrombin

* The correction for sampling differences in diagnosis undertaken at various points does not correct for this difference.

† The sex difference for myocardial infarction cases is an exception to this statement for 82 per cent of the Tromexan group in this category were males as compared with 70 per cent of the dicumarol cases. This difference probably did not affect the conclusions since in the previous dicumarol study no statistically significant difference was found between the sexes in their incidence of thromboembolic complications.

* This curve was based on the medians of findings for various dilutions for normal blood samples tested by the cooperating hospitals using the Link-Shapiro modification of the Quick method.

times in seconds from hospital to hospital.* For example, 60 seconds, meaning in this study 6 per cent, was approximately equivalent at the time of the study to 49 seconds at Bellevue and 96 seconds at the Mayo Clinic. Similar differences occurred with respect to the meaning of the "therapeutic range" within which physicians cooperating with the project were advised to keep prothrombin times. On the basis of the findings of the previous dicumarol study,[18] this range was defined as 25 to 39 seconds on the composite curve or 23 to 11 per cent in terms of prothrombin activity.† The approximate equivalent of this range at Bellevue was 22 to 33 seconds and at the Mayo Clinic, 32 to 56 seconds. If the implications of the present findings are not to be missed or misinterpreted, each reader will need to translate the seconds as reported in this article into their equivalent for the laboratory with which he deals. This can be done by comparing the dilution curves run for normal blood at various control times by his laboratory with the percentages reported on line two in the foregoing table.

TABLE 3.—*Number of Seconds for Each Cooperating Hospital Approximately Equivalent on the Average at the Time of the Study to Given Seconds on the Composite Curve Developed Previously for Use in the Dicumarol Study*

	Composite Curve			
In seconds	17 (upper limit of normal)	25–39 ("therapeutic range")	50–59	60 or more
In per cent prothrombin activity	58% or more	23%–11%	7%–6(.3)%	6(.2)% and under
	Average Equivalents in Seconds in Laboratories of Cooperating Hospitals*			
Bellevue, *N. Y.*	15	22–33	42–48	49 or more
Henry Ford, *Detroit*	17	24–37	50–54	55 or more
Jackson Memorial, *Miami*	16	24–40	51–59	60 or more
Lakeside, *Cleveland*	18	34–68	90–97	98 or more
Mayo, *Rochester*	21	32–56	86–95	96 or more
The New York Hospital, *N. Y.*:				
General laboratory	18	27–43	59–74	75 or more
Research laboratory	16	26–43	56–67	68 or more
Pennsylvania, *Philadelphia*	18	31–50	60–64	65 or more

* Computed from dilution curves for normal blood furnished by hospitals.

* The use of percentage will not improve this situation in a given hospital unless the control and each reading are first carefully determined in seconds. Errors in this determination will be perpetuated when converted into percentage which is essential only for comparison with other laboratories.

† The recommendation was based on the findings with respect to the incidence of thromboembolic complications and hemorrhages per 1000 days of dicumarol therapy at different prothrombin time levels. It was found that prolongation beyond 25 seconds was necessary to afford the patient maximum protection against thromboembolic complications, but that prolongation beyond 40 seconds afforded no increased protection. Since the risk of hemorrhage was found to increase rapidly above 40 seconds, 40 seconds was defined as the upper limit of the therapeutic range.

EFFECTS ON THE PROTHROMBIN TIME

Previous experience, as mentioned before, has shown that Tromexan acts with greater rapidity than dicumarol, and that its effect is more rapidly dissipated after cessation of therapy. These findings were confirmed in the present study. Patients followed at The New York Hospital (where the time of the initial dose was definitely known) may be used to illustrate the difference in response pattern. Of 26 patients receiving either 1500 or 1800 mg. of Tromexan on the first day, 12 (or 46 per cent) rose above 20 seconds in 24 hours and 24 (or 92 per cent) rose above 20 seconds by 48 hours. Of 23 cases receiving 300 mg. of dicumarol on the initial day only six (or 26 per cent) were above 20 seconds in 24 hours and only 14 (or 61 per cent) had risen above this level in

24 hours.* Patients who were in shock or manifested hepatic or renal dysfunction were excluded from both groups. In the Tromexan group only patients who received either 1500 or 1800 mg. of the drug were included as an initial dose of 1200 mg. was frequently insufficient to effect a good prothrombin response. Work performed at Bellevue Hospital by Dr. Erwin Nydick (unpublished) indicated that single doses of 1500 mg. and 1800 mg. of Tromexan (given to patients with nonthromboembolic illnesses) showed a wide range of response in prothrombin times. Wide variation in responses to a single dose of dicumarol have been frequently encountered and reported.[19] This variability serves to emphasize the fact that dosage requirements of either drug must be based on consecutive prothrombin readings.

On the other hand, the fall in the prothrombin time toward normal after cessation of Tromexan is notably more rapid and predictable than after dicumarol. Not infrequently the prothrombin time has been noted to continue rising after dicumarol is stopped whereas this was rarely observed following discontinuance of Tromexan. In this series of 263 instances tabulated in sequence where Tromexan was omitted for one day, the prothrombin time showed a definite decrease in all cases but 17 on the following day. Of these 17, five were unchanged, and in 12 the prothrombin time rose. In two of these rises the increase was slight. Five of the 12 cases had received unusually large doses, two had renal disease, one was hypersensitive to small doses, and in two the rises remained unexplained. In a similar setting of 113 cases of dicumarol cessation, the prothrombin time fell in 70, remained the same in four, and rose in 30 (of which one case had mild renal disease, and one had hepatomegaly, the remaining being unexplained). These findings illustrate the dependability with which the effect of Tromexan diminishes over a 36 hour period, but in uncommon instances some elevation of the prothrombin time may persist for a number of days. There were at least four instances in this series of elevations above 40 seconds that stayed above this level three to five days without further Tromexan. Three showed mild renal disease and one of these congestive hepatomegaly. Data for the evaluation of the fourth were lacking. This phenomenon is not uncommon in the case of dicumarol and no attempt was made to analyze data on its frequency.

As a further test of the speed of drop with Tromexan, all instances when prothrombin times reached or exceeded 60 seconds on the composite curve (6 per cent or less) under both Tromexan and dicumarol were noted. In those instances in which the patient was not influenced by heparin or Paritol, received no anticoagulant on the first day at 60 seconds, and was not treated with vitamin K or blood, the times the first day after this first reading of 60 seconds or more were tabulated. Sixty-one such qualifying instances were found during Tromexan therapy but only 11 during dicumarol therapy. On the day following the first observation of these excessive prolongations, 30 or half of the 61 Tromexan cases showed times below 25 seconds, and 52 of the 61 had dropped to below 40 seconds or out of the zone of excessive hemorrhage risk. Only four remained above 60 seconds. In contrast, 6 of the 11 available dicumarol cases remained above 60 seconds the day following under similar circumstances, and none had dropped below 25 seconds. While this dicumarol sample is much too small, the findings are consistent with clinical experience with this drug and may be assumed representative. Anticoagulant therapy must take into account this great difference in the probable prothrombin level the day following excessively prolonged times.

The time of return of the prothrombin time to normal levels after complete cessation of therapy was determined by daily prothrombin times in 51 of the Tromexan cases whose time on the day of the last dose was in the "therapeutic range" (between 25 and 39 seconds, or 23 per cent to 11 per cent). Corresponding data were available for only 11 of the dicumarol cases. (Prothrombin readings for most patients were terminated before the base line was reached.) All but 11 of the 51 Tromexan cases with usable records showed normal times (17 seconds, or 58 per cent or more) by the third

* For graphic presentation of these cases see figure 16 in reference 20.

day after the last dose, the maximum time for the return being six days and the average two and nine-tenths days. The corresponding average for the 11 dicumarol cases was five and one-tenth days and the maximum, eight days. This average figure compares well with the four and seven-tenth average number of days to normal for the study of dicumarol in myocardial infarction based on 78 cases with records to normal and times between 20 and 39 seconds on the day of the last dose. In this former study with dicumarol the maximum time for the return was 13 days instead of eight.[18] In view of the rapidity of the fall with Tromexan from high levels, the failure of Tromexan cases to return immediately to normal may seem surprising, but it is common experience that the prothrombin time may linger a few seconds above the base line for some time after a previously rapid fall. This may actually be protective rather than undesirable.

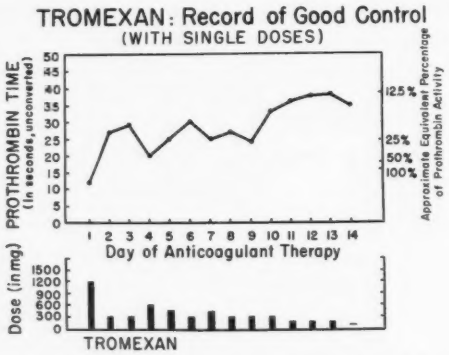

FIG. 1. Case illustrating good control of prothrombin times after rapid prolongation following a small initial dose of Tromexan given for acute thrombophlebitis. (Note slight fluctuations in daily prothrombin times. Drug was administered in a single daily dose.)

Lability of prothrombin times in Tromexan treated patients was noted in a number of the case reports submitted to us. Barker[16] and Wright [20] have commented upon this in the literature. This lability is seen in the sudden unpredictable rises in the prothrombin time that occasionally occur during an apparently stabilized regimen. Figure 1 illustrates a case in which satisfactory control was consistently maintained and figure 2 illustrates a case in which such an "escape" occurred. In the latter case, as in most such instances, immediate cessation of therapy at that point resulted in a rapid regression of the prothrombin time.

In connection with lability studies, all rises above 60 seconds were counted. A total of 105 rises above 60 seconds occurred during therapy with Tromexan only among 333 patients receiving Tromexan at some time and 25 during therapy with dicumarol only among 226 patients receiving dicumarol at some time (mixed drug cases counted under both drugs). Forty-four per cent of the dicumarol rises were treated with vitamin K or blood, but only 14 per cent of the Tromexan rises received similar treatment. A total of 118 days under Tromexan only and 42 days under dicumarol only were known to be at 60 seconds or over. Thus on the average the times remained 60 seconds or over one and one-tenth days under Tromexan and one and seven-tenth days under dicumarol. The contrast would probably be greater except for the more intensive therapy of the dicumarol "escapes."

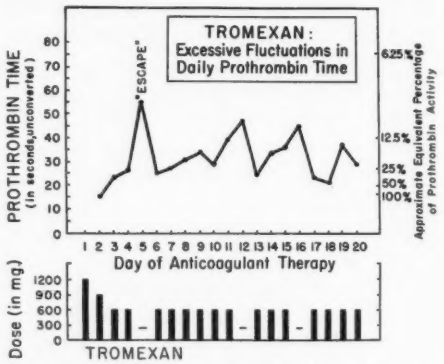

FIG. 2. Case demonstrating sudden changes in prothrombin times with single doses in a patient receiving Tromexan for acute thrombophlebitis. [Cessation of drug for one day resulted in prompt fall in the next prothrombin time. Note lack of response to small (1200 mg.) initial dose.]

Since these undue elevations constitute a potential hemorrhagic hazard to the patient, the comparative incidence of all elevations above 50 seconds in the two anticoagulants also was studied. Before tabulation, prothrombin times were converted to a comparable basis and days under two anticoagulants at the same

t me and the first day of therapy were omitted. l nder both drugs the proportion of prothrom- b n times of 50 seconds or more was slight. Of 3 927 days of therapy with dicumarol only and h ving usable prothrombin times, 1.9 per cent w ere 50 seconds or more (7 per cent or less), w hereas, of 5,965 similar days on Tromexan o ly, 3.3 per cent were 50 seconds or more.*

Because it was thought that increasing experience with Tromexan might lead to a decrease in the number of these elevations, the Tromexan sample for each hospital was divided chronologically into cases treated during the first and second half of the study period. No differences appeared in respect to the avoidance of dangerous prothrombin times in the two periods. However, when the Tromexan cases were analyzed according to whether they received single or divided daily doses of Tromexan, the results were more striking. They are shown graphically in figure 3. Patients maintained largely† on single daily doses had 3.6 per cent of their times at 50 seconds or more; patients on a mixed regimen, 2.6 per cent of their times at these elevations; and patients largely on divided doses, only 0.4 per cent of their times in this range. In this last group actually only one reading exceeded 49 seconds—a remarkable record of stability. Unfortunately, patients largely on divided doses were a very small group and received only 253 days of Tromexan therapy, with the result that the finding of improved stability cannot be considered conclusive at this time. Most of the patients receiving dicumarol were treated only with single daily doses. The record for such patients showed that 1.8 per cent of their times were in this range, a record midway between the single and divided dose rates for Tromexan. The results, if confirmed by further clinical experience, suggest that Tromexan therapy using divided daily doses may offer to the practitioner the advantages of the quick rise and fall characteristics of Tromexan without its disadvantage of uncontrollability. Further trial with divided doses is indicated.

* The data refer to total days at 50 seconds or more, not to the number of separate rises. In the case of Tromexan high times fall rapidly again to lower levels, as previously demonstrated, whereas in the case of dicumarol, they tend to persist several days. Consequently, the larger number of separate instances of rises that occurred in the case of Tromexan were partially counteracted in the above rates by their shorter duration.

† "Largely" was defined as 80 per cent or more of the time under anticoagulant therapy.

Thromboembolic Complications

The cooperating hospitals were asked to watch carefully for, and to report in detail, all thromboembolic complications occurring both in and outside the heart during the period of observation for each case. After a critical review, such thromboembolic complications as had been diagnosed on the basis of clinical evidence, signs, or symptoms as definite or probable were included in the counts. Those appearing improbable on such a basis and those undiagnosed until autopsy studies revealed them were excluded since protocols were available for only a small proportion (3 per cent) of the total cases.

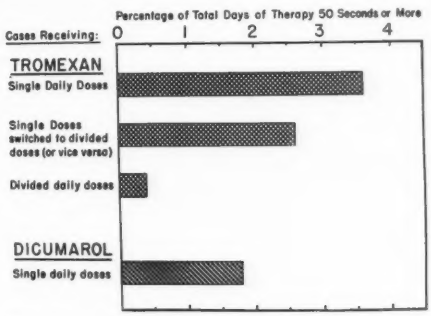

FIG. 3. Percentage of total days spent under the influence of Tromexan and dicumarol only and having usable prothrombin times of 50 seconds or more (7 per cent or less) among patients receiving Tromexan in single and/or divided daily doses and among patients receiving dicumarol in single daily doses.

By these criteria, a total of 59 thromboembolic complications occurred during the period of observation. Of these, one occurred before therapy could be instituted,* and 17, after the termination of anticoagulant therapy. The latter will be discussed separately. No

* Since cases were classified by the thromboembolic condition for which anticoagulants were first prescribed, there was little opportunity for complications prior to anticoagulant therapy.

complication occurred on days when patients were protected by heparin or Paritol. One complication, a myocardial infarction, occurring when the patient was influenced by both Tromexan and dicumarol, cannot be allocated to either anticoagulant and is therefore omitted from all further counts. The other 40 complications occurred during either dicumarol or Tromexan therapy and will be discussed in detail.

The total counts converted to a day rate basis* are shown in figure 4. On the 6,642 days when patients were under the influence of Tromexan as the only anticoagulant, a total of 25 thromboembolic complications occurred, a rate of 3.8 per 1000 days of therapy. On the

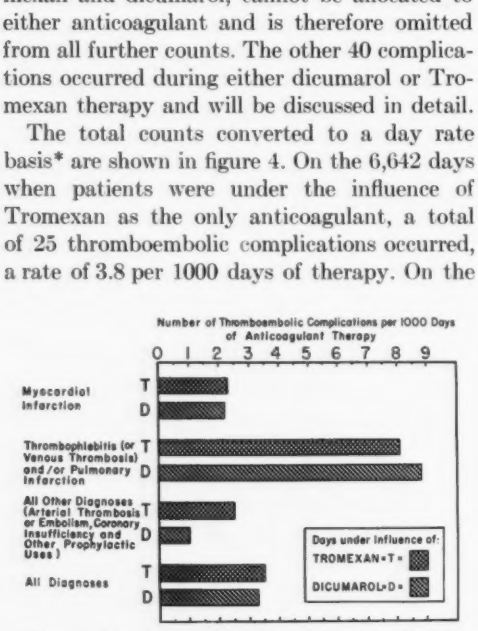
Number of Thromboembolic Complications per 1000 Days of Anticoagulant Therapy
0 1 2 3 4 5 6 7 8 9
Myocardial Infarction
Thrombophlebitis (or Venous Thrombosis) and/or Pulmonary Infarction
All Other Diagnoses (Arterial Thrombosis or Embolism, Coronary Insufficiency and Other Prophylactic Uses)
All Diagnoses
T
D
Days under influence of:
TROMEXAN=T=
DICUMAROL=D=

FIG. 4. Number of thromboembolic complications of all types occurring on days when patients were under the influence of Tromexan or dicumarol only per 1000 days of corresponding type of anticoagulant therapy, by diagnosis (corrected rates).

5,006 days when dicumarol was the only anticoagulant, a total of 15 complications occurred, a rate of 3.0 per 1000 days of therapy.† The rates are surprisingly close considering the variety of component diagnoses included and the number of other uncontrolled variables.

In order to ascertain the effects on these total rates of certain differences in the Tromexan and dicumarol samples previously noted, statistical corrections were made in these foregoing thromboembolic rates both for the larger proportion of thrombophlebitis cases and for the larger proportion of therapy in the early weeks characterizing the Tromexan group * These corrections brought the total complications during Tromexan therapy to 3.5 and the dicumarol rate to 3.3 per 1000 days. The remaining difference of 0.2 complications per 1000 days of therapy cannot be considered significant either statistically or medically.

For myocardial infarction cases, the most homogeneous diagnostic group in the sample, the day rates for the two anticoagulants after similar corrections for sampling differences were almost identical, namely 2.3 thromboembolic complications per 1000 days of Tromexan therapy as compared with 2.2 per 1000 days for dicumarol therapy (see figure 4).† While this very close similarity is no doubt a chance coincidence, the two drugs would appear to be about equally effective as prophylaxis against thromboembolic complications, at least in this condition. The myocardial infarction rates are also low in a comparative sense since they are about one-third below the corresponding rate of 3.1 per 1000 days of therapy for the treated group in the earlier study of dicumarol therapy in coronary thrombosis with myocardial infarction[18] and far below the corresponding rate of 12.6 for the control group in that series for days of their illness corresponding to the period of therapy for the treated group. In this former study, many physicians were using dicumarol for the first time and hesitated to administer adequate doses, with the result that prothrombin times were too low for adequate protection in a substantial proportion of cases.

For the other diagnostic groups shown in figure 4, lack of close comparability in com-

* Day rate here refers to number of complications per 1000 days of Tromexan and dicumarol therapy.

† When the "special" (nonalternate) cases are excluded, the rate for the alternate series during Tromexan therapy becomes 4.2 and that during dicumarol therapy becomes 3.5 per 1000 days while the rate during Tromexan therapy for the "special" Tromexan series is changed to 3.1.

* The method of correction used involved retaining the specific rates by week of illness and diagnostic groups actually found for dicumarol and Tromexan, but giving these specific rates the same proportionate weights in the total rate for each anticoagulant. The procedure is similar to that used in the computation of standardized birth and death rates. The weights used were based on the distribution of the total sample days of therapy for both anticoagulants.

† The corresponding uncorrected rates were 2.2 per 1000 for Tromexan and 2.2 per 1000 days for dicumarol.

ponents and small numbers handicap conclusions. Pulmonary infarction was combined with thrombophlebitis and venous thrombosis because of the frequency with which they were found together in a double diagnosis. The rates of thromboembolic complications for both Tromexan and dicumarol for this group were similar but relatively high, 8.1 and 8.8 per 1000 days, respectively, after correction for the major sampling differences.* In general, thrombophlebitis in patients receiving adequate Tromexan therapy appeared to resolve as rapidly and with as few sequelae as those treated with dicumarol.

The remaining group consists largely of patients with whom anticoagulant therapy was used for prophylactic purposes, especially with evidence of coronary insufficiency, with suspected but not clear-cut attacks of coronary thrombosis, and postoperatively. Included are also a few cases of arterial embolism and one of cerebral thrombosis. The incidence of complications in these cases was exceedingly low, the corrected rates being only 2.5 complications for Tromexan and 1.0 for dicumarol per 1000 days of therapy.† In this group, as in the total sample, the rate of complications with Tromexan is slightly higher than the rate with dicumarol, but comparability between these varied groups is not fully assured and chance factors may well account for such slight differences. In addition, a problem of control under Tromexan entered in which will be discussed later.

Because of the varying duration and timing of anticoagulant therapy from case to case and the varied extent of supplementation with heparin or Paritol, cases are not strictly comparable with one another. Therefore, rates have been based on days of anticoagulant therapy rather than on case counts, a type of rate doubtless new to some readers. In visualizing the meaning of these rates, the physician is justified in thinking of 1000 days as approximately equivalent to 50 cases treated with anticoagulants for 20 days each, a typical period of therapy. On this basis the above rate of 2.2 complications per 1000 days under anticoagulants for the myocardial infarction group may be thought of as roughly equivalent to four or five complications *during therapy* per 100 cases treated for about three weeks each, or one to each 20 cases so treated. This rate is obviously lower than the rate of 8.5 complications per 100 cases which occurred during anticoagulant therapy in the treated group of the earlier study of the Committee,[18] and 34.9 complications per 100 cases occurring in the untreated group during a comparable period of their illness.* These rates omit the usual quota of complications before and after anticoagulants included in some figures in other studies.

In order to think directly in terms of patients or case rates in the present study, one must omit the 45 patients who received both Tromexan and dicumarol (referred to as the "mixed drug" cases and included in figure 4), together with 11 complications occurring in these cases. With these omissions, the complications occurring under dicumarol only were distributed by diagnosis as follows: seven complications (or 6.6 per 100) in the 106 cases of myocardial infarction and four (or 11.4 per 100) in the 35 cases of pulmonary infarction and/or thrombophlebitis or venous thrombosis. No cases receiving dicumarol only in any other diagnosis developed any complication. The complications under Tromexan were as follows: nine complications (or 6.5 per 100) in the 139 myocardial infarction cases treated with Tromexan, seven (or 9.2 per 100) in the 76 pulmonary infarction and/or thrombophlebitis or venous thrombosis cases, and two (or 2.7 per 100) in the 73 cases in the "all other" diagnoses group. Since the periods of therapy were not standardized for the two drugs, the case

* The corresponding uncorrected rates were 8.6 for Tromexan and 8.3 for dicumarol. These uncorrected rates include one cancer case that developed three complications under dicumarol and three under Tromexan. If this extreme case is omitted, the rates become 6.7 complications for Tromexan and 4.9 for dicumarol per 1000 days of therapy.

† The corresponding uncorrected rates were 2.7 for Tromexan and 1.0 for dicumarol per 1000 days.

* A rate that is strictly comparable cannot be computed for this previous study since, in the original dicumarol study, cases received an average of 28 days instead of 20 days of therapy with dicumarol only. Strictly comparable figures for the original dicumarol study would be slightly lower, perhaps 7.5 instead of 8.5 for the treated group.

counts cited are not believed in this situation to be a fully definitive basis for the evaluation of the protective capacity of the two anticoagulants.*

A wide variety of thromboembolic complications both inside and outside the heart have been included in the reported totals. Specific rates by type of complication are not justified because of the low counts, but a listing will illustrate the types included. On the 5,006 days when dicumarol was the only anticoagulant in effect, the following types of complications occurred: one new myocardial infarct, two extensions of myocardial infarcts, five pulmonary infarcts (or emboli), six new episodes or recurrences of thrombophlebitis, and one embolus to the juncture of the left femoral and profunda femoral artery. On the 6,642 days when Tromexan was the only anticoagulant in effect, the complications occurring were as follows: three extensions of myocardial infarctions, five pulmonary infarcts (or emboli), 11 new episodes or recurrences of thrombophlebitis, four cerebral emboli, one renal embolus, and one extension of a cerebral arterial thrombosis.† In view of the small numbers and variations in the previous history of the patients, differences in the distribution cannot be attributed to the type of anticoagulant employed.

Analyses by such factors as age and sex were precluded by the small numbers within most diagnostic subgroups, but a breakdown was attempted by time of occurrence in relation to the date of onset of the original thromboembolic conditions for which anticoagulants were given. The results are reported in figure 5. In all the diagnostic groups the incidence of thromboembolic complications under therapy was highest during the first two weeks of therapy. In the myocardial infarction group Tromexan and dicumarol showed rates per 1000 days of therapy of 3.0 and 4.9 respectively during the first two weeks after the attack. During the third and fourth weeks the Tromexan and dicumarol rates were 1.8 and 1.6 per 1000 respectively. These rates compare closely with the experience in the dicumarol study,[18] for which the corresponding rate for the first two weeks was 4.5 complications per 1000 days of dicumarol therapy and 2.1 for the third and fourth week.

Since the maximum risk of thromboembolic complications clearly falls in the first and second week after the onset of the original thromboembolic condition, the more rapid initial prolongation of prothrombin time possible with Tromexan probably has distinct medical value. Unfortunately, a statistical evaluation

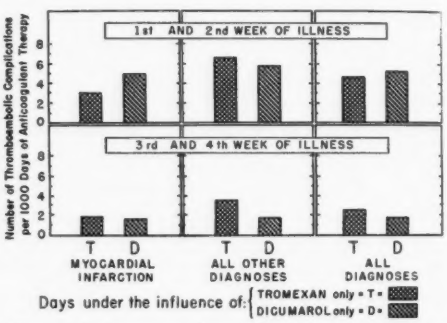

FIG. 5. Number of thromboembolic complications of all types occurring on days when patients were under the influence of Tromexan or dicumarol only per 1000 days of corresponding type of anticoagulant therapy, by diagnosis and week of illness (cases with unknown date of onset and therapy after the fourth week omitted).

of the reduction in risk of thromboembolism during the first three or four days of anticoagulant therapy was not feasible because a large proportion of the cases (32 per cent) received supplemental protection with heparin or Paritol, primarily in this early period. This was a sufficient proportion to blur recognition of differences between the drugs during this early period, particularly since 37 per cent of the dicumarol cases but only 28 per cent of the Tromexan cases received such supplementation. In spite of this lesser supplementation, however, the complication record for Tromexan during the first two weeks in myocardial infarction cases, as shown in figure 5, is somewhat better than the dicumarol record when supplementation days are excluded, while in the third and fourth week the rates for the two are

* The periods of observation and degree of supplementation also were not standardized, it being the intention to leave the hospitals complete freedom in these respects. The groups also are small and not fully homogeneous.

† The foregoing counts include mixed drug cases.

about the same. Without more rigid controls and a larger number of cases, it is impossible to be certain whether this difference results from the more immediate protection afforded by Tromexan or some extraneous factor, but the difference is suggestive of the advantages of a rapid rise at the outset of therapy.

When the onset of the thromboembolic complications was correlated with the prothrombin times at the time of the episode, it was found that only 3 of the 12 complications under dicumarol with times available for the day of onset* occurred with prothrombin times below 25 seconds (24 per cent or above) on the day of the complication. On the other hand, 16 of the 22 complications in the Tromexan group with times for the day of onset had levels below 25 seconds on that day. This contrast suggests that the slightly higher incidence of complications for some diagnoses under Tromexan was related to the difficulty of controlling prothrombin levels with this anticoagulant and not to any intrinsic failure of Tromexan to prevent thrombosis at adequate prothrombin levels. This experience dramatizes the need for close watchfulness against rapid drops during Tromexan therapy.

Of the six cases in the Tromexan group with thromboembolic complications developing at prothrombin times of 25 seconds or above, only one occurred when the prothrombin time also had been maintained at a level of 25 seconds or more for the two preceding days. This one "true failure" of Tromexan therapy† consisted of the recurrence and progression of thrombophlebitis in the presence of carcinomatosis—a well-known cause for failure of anticoagulants to inhibit thromboembolic complications.[20, 21] By this same three-day sequence test, however, there were six "failures of anticoagulant therapy" in the case of dicumarol, one of which again was a cancer case.‡ Omitting complications in cancer cases, the total for the entire series becomes five "true failures," a small number indeed for thromboembolic complications in about 12,000 days of anticoagulant therapy.*

Not included in the foregoing counts were 17 thrombembolic episodes occurring after anticoagulants were terminated, of which 15 occurred within 16 days or less of the end of anticoagulant therapy. The interim between anticoagulant and complication was deemed the number of days after the prothrombin time had returned to normal or, if these were not given, as starting after an arbitrarily chosen number of days of residual anticoagulant effect (four days for dicumarol and one day for Tromexan). This interval is of particular interest. Six complications followed a last dose of dicumarol by 3, 6, 7, 8, 9 and 16 days after the end of anticoagulant influence. The other nine followed a last dose of Tromexan by 2, 2, 2, 4, 6, 6, 7, 8 and 15 days after the actual or estimated end of influence. Inspection of the duration of therapy indicates that at least six of these cases had been treated for an inadequate length of time and that therefore some recurrence could be anticipated. Nevertheless, these complications fall within rather distinct time periods for each anticoagulant. The omission of the 15 and 16 day episodes leaves a range for dicumarol from three to nine days and an average of seven days and a range for Tromexan of two to eight and an average of five days, a difference that is consistent with the nature of the two anticoagulants.† Thromboembolism after such intervals is not too infrequent a phenomenon. It has been suggested

* Times for the day of onset for three complications under dicumarol and three under Tromexan were not reported.

† Failure in the sense that the prothrombin time was completely within the therapeutic range during a period when a fresh thrombus could probably form.

‡ One complication under Tromexan and two under dicumarol lacked times for one of the two preceding days and therefore could not be classified.

* Conclusions regarding the relative incidence of "true failures" under the two anticoagulants should be withheld because (1) the definition of a failure is arbitrary, (2) failures diagnosed only at autopsy are omitted, and (3) the number of readings below 25 seconds and the number in the therapeutic range were not tabulated.

† When one considers that the scattered residual effects of Tromexan persist from 1–6 days and those of dicumarol, 1–13 days and that arbitrary estimates of 1 and 4 days were usually used in computing the above intervals, it is quite possible that most of these complications actually occurred almost immediately after the termination of anticoagulant influence rather than after an interim period.

that this may be due to a "rebound" phase of hyperprothrombinemia or hypercoagulability, although this has not been proven in vitro. The shorter interim for Tromexan and the larger for dicumarol may suggest such a possibility. At least as likely is the possibility that the underlying disease process had not subsided during the time anticoagulant therapy was continued. The experience of the authors and others[21] has led to the suggestion that in terminating therapy anticoagulant doses should be tapered off gradually but the value of this has not been critically established. Since these recurrences and other thromboembolic complications are especially apt to occur after short courses of anticoagulant therapy, anticoagulants should certainly be continued until the risk of recurrence of thromboembolic episodes is minimal.

Hemorrhages during Anticoagulant Therapy

Hemorrhage, an extension of the therapeutic effects of anticoagulants, represents the limiting factor in the clinical use of these drugs. Other factors being equal, the incidence of bleeding in any large series under an anticoagulant reflects the controllability over the agent, as excessive prolongations of the clotting process result in a marked increase in the incidence of bleeding. (In small series of patients the variables are so great as to render any conclusions invalid.)

Data concerning hemorrhages in this series were obtained by compiling descriptions of hemorrhages clinically observed and the analysis of laboratory data on microscopic hematuria and melena. Hemorrhages diagnosed only at autopsy were excluded. A total of 125 hemorrhages were reported on the master forms as occurring during the period of observation. Of these, 24 began when the patients were not on anticoagulant therapy and another five occurred when heparin or Paritol were in effect and are excluded as not pertinent to the problem under study. One other, occurring when both Tromexan and dicumarol were in effect, had to be omitted since it could not be allocated to either anticoagulant. The remaining 95 of these occurred when Tromexan or dicumarol alone was in effect. These were studied intensively. Figure 6 presents the over-all picture with special emphasis on the relation of the episodes to anticoagulants. The group termed "episodes not related to anticoagulants" consists of 10 episodes under Tromexan and seven under dicumarol that were due to other causes that were sufficient to explain the full extent and severity of the hemorrhage. The rates per 1000 days of therapy were similar and serve only to confirm the approximate comparability of the groups in respect to susceptibility to bleeding. The remaining episodes were believed to be related to anticoagulant therapy. Those without other causes competent to produce hemorrhages and believed under the circumstances to be caused by anticoagulant therapy, were classified as "due to anticoagulants." Those arising from a known hemorrhagic site but in which the bleeding appeared aggravated by, precipitated by, or prolonged by, anticoagulant therapy were classified as "aggravated by anticoagulants." The resulting rates, based on 6,642 days of therapy with Tromexan only and 5,006 days of dicumarol only, showed the rate for gross hemorrhages due to anticoagulants to be 2.3 per 1000 days for Tromexan and 1.8 per 1000 days for dicumarol. Episodes aggravated by anticoagulants showed a rate of 2.4 gross bleeding episodes per 1000 days for Tromexan and of 1.2 similar episodes per 1000 for dicumarol.

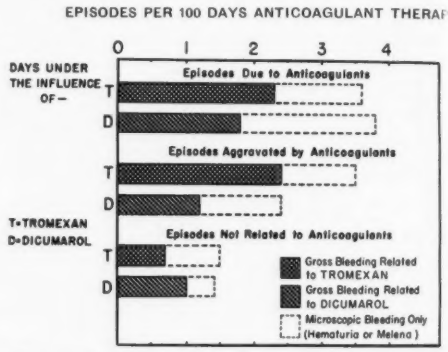

Fig. 6. Number of bleeding episodes due to, aggravated by, or unrelated to, anticoagulant therapy beginning on days when patients were under the influence of Tromexan or dicumarol per 1000 days of corresponding type of anticoagulant therapy.

The total for Tromexan for gross episodes related to anticoagulants is therefore 4.7 per 1000 days and that for dicumarol, 3.0 per 1000 days.* The difference in each case is small, amounting to less than 2 episodes per 1000 days of anticoagulant therapy, or approximately 3 to 4 additional episodes per 100 patients treated for 20 days each. Evaluation of this small difference is difficult.

As a first step in appraisal, statistical corrections for certain known differences between the two samples were undertaken for hemorrhage rates in the same manner previously described for thromboembolic complication rates.† It was found that these corrections made only very minor changes in the rates quoted.‡ The rate for gross hemorrhages related to Tromexan was raised from 4.7 to 4.8 per 1000 days while the gross rate for dicumarol remained unchanged. Other changes were similarly small. Clearly those obvious sampling differences for which corrections were feasible do not account for the differences noted.

A further test indicated that the difference also was not produced by the addition to the sample of the Tromexan cases collected without alternation with dicumarol since the amount of the difference remained about the same when these "special" (nonalternate) cases were excluded.*

Whether the difference in corrected rates for gross hemorrhages related to the two anticoagulants of 1.8 per 1000 days was due to chance was also tested. The probabilities were found to favor explanation in terms other than chance,† but explanation on a chance basis could not be ruled out with the degree of certainty that is conventionally implied by the term "statistically significant".‡ Nevertheless, since such a difference would become statistically significant if it persisted in a larger sample, it does not appear sound to pass it over without a full examination of the components which comprise these totals.

It should be noted first that the difference

* For comparison of rates with the dicumarol study, microscopic hemorrhages must also be included and original diagnoses other than myocardial infarction omitted. When this is done, the Tromexan rate becomes 6.7 and the dicumarol rate becomes 6.3 per 1000 days of anticoagulant therapy. Both these rates are about double the comparable rate of 3.3 hemorrhages per 1000 days of anticoagulant therapy in the original dicumarol study. The higher rate probably reflects primarily the higher prothrombin times maintained in the present study and secondarily, perhaps, better reporting of hemorrhages.

† See first footnote, second column, p. 498, for explanation of the method employed.

‡ The process of correction left the microscopic hemorrhage rate for Tromexan unchanged (2.4 per 1000 days) and changed the dicumarol rate from 3.2 to 3.3 per 1000 days. The total rate for Tromexan (gross plus microscopic) became 7.2 instead of 7.1 per 1000 and the total rate for dicumarol, 6.3 instead of 6.2 per 1000. All rates refer to hemorrhages due to, aggravated by, or precipitated by, anticoagulants per 1000 days of anticoagulant therapy of a given type.

* Among the alternate series cases, the number of gross hemorrhages related to Tromexan per 1000 days of therapy with Tromexan only was found to be 5.1 and the corresponding rate for dicumarol to be 3.5 per 1000. The "special" (nonalternate) cases showed a rate of 3.9 for Tromexan. The 21 dicumarol cases in the nonalternate group showed no gross hemorrhage but the rate is meaningless in this case because of the small number in the group.

† The chances were found to be about 9 per 100 that a difference equal to the difference (as corrected below) and in this direction would occur on a chance basis. To apply the test it was necessary for statistical reasons to convert the corrected rates into a true proportion (the proportion of total days of therapy on which hemorrhages began) by deducting for two or more hemorrhages beginning on the same day. This procedure reduced the difference between the two anticoagulants since three hemorrhages under Tromexan began on the same day in the same patient, whereas there was no more than one gross hemorrhage on the same day in the case of dicumarol. The test necessarily assumes also that the record for each day is independent of that for every other day, which is not, strictly speaking, true since more than one day was observed for each patient; corrections for this characteristic of the data were not feasible, but if undertaken would have reduced slightly the probabilities of significance quoted.

‡ The conventional definition requires that there be less than 1 or 2 chances (or at least less than 5) in 100 that the difference could occur on a chance basis before the difference is termed "statistically significant"; however, the confidence level adopted is the responsibility of the authors and the choice should rest ultimately on the direction in which an erroneous interpretation would have the more serious consequences.

appears only with respect to gross hemorrhages. From figure 6, where microscopic bleeding is shown by dotted extensions of each bar, it is apparent that the difference does not extend to microscopic bleeding, for a larger proportion of the total hemorrhages under dicumarol than under Tromexan were microscopic in character.* Unfortunately, the rates for microscopic hemorrhages are greatly dependent on the frequency of laboratory examinations of urine and stools and there is no assurance that the two groups were examined in this manner with equal frequency. Therefore no great reliance should be placed on these dotted extensions, which in any case represent in most cases only minor and insignificant bleeding. Furthermore, a large experience with anticoagulants has demonstrated that microscopic hemorrhages are usually of little or no importance. For this reason, although microscopic bleeding is shown by dotted extensions in all charts, the textual discussion refers largely to gross bleeding.

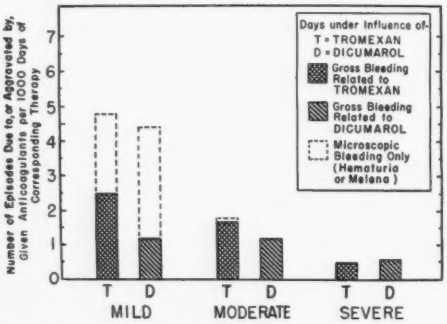

FIG. 7. *Severity of Bleeding Episodes.* Number of mild, moderate, and severe bleeding episodes due to, or aggravated by, anticoagulant therapy beginning on days when patients were under the influence of Tromexan or dicumarol per 1000 days of corresponding anticoagulant therapy.

Figure 7 presents graphically the severity of the bleeding episodes. Those termed "mild" include microscopic hematuria and occult melena and slight or transient but visible bleeding from any site. "Moderate" bleeding includes visible and more prolonged bleeding, but bleeding often untreated and without threat to life. "Severe" bleeding represents episodes that were excessive and dangerous and often required emergency treatment. When microscopic hemorrhages were included, 68 per cent of the bleeding episodes under Tromexan and 71 per cent of those under dicumarol were mild. The difference is of no consequence. Again, gross bleeding in both the mild and moderate categories was somewhat more in evidence under Tromexan than under dicumarol, but the difference was greater in the mild category of gross bleeding. Three severe hemorrhages related to anticoagulants were diagnosed under each drug. The three under Tromexan were all considered due to the drug.* In the case of the three for dicumarol, other underlying pathology was present in two. Fatal hemorrhages and hemorrhages diagnosed at autopsy only are discussed elsewhere.

The types of bleeding that compose these totals are shown in figure 8. It will be noted that hematuria is the commonest manifestation of bleeding from both drugs and that more than half of the hematuria episodes were microscopic only. Both the gross and microscopic rates for hematuria are remarkably close for both drugs. The contrast in hemoptysis is less significant than would appear, for three of the five cases that constitute the Tromexan column for this type of bleeding occurred in the presence of pulmonary infarction. All were mild except one which required treatment with vitamin K and whole blood. Tromexan showed slightly more severe gastrointestinal bleeding than dicumarol, although there was a greater reported incidence of occult (guaiac test) bleeding with dicumarol. The difference in epistaxis is a matter of five episodes versus one, mostly mild. For bleeding of other types the rates are identical. This miscellaneous group includes

* When laboratory reports showed 15 or more red blood cells per high power field microscopic hematuria was recorded, the period from the beginning of observation of hematuria until the urine had cleared being counted as one episode, not several, regardless of the number of laboratory observations. The procedure was similar with melena, ordinarily only 2 plus guaiac or over being counted as occult melena.

* Counts exclude one case treated with Tromexan showing severe hemorrhage in several sites at autopsy (see *Deaths Occuring during Study*), since this bleeding was not diagnosed clinically.

uterine bleeding related to anticoagulants, bleeding from sites of operations or from hematoma, bleeding gums, and one each of the following: cerebral hemorrhage, ecchymoses, and petechial hemorrhage.

Gross hemorrhages due to anticoagulants were also compared as to duration,* measured roughly in terms of the number of different days on which bleeding was in evidence. The averages were practically identical for the two drugs, two and four-tenths days for dicumarol and two and three-tenths days for Tromexan. In general, when hemorrhage appeared and

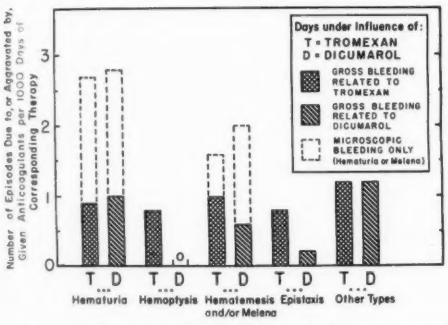

FIG. 8. Number of bleeding episodes of specific types beginning on days when patients were under the influence of Tromexan or dicumarol only and considered due to, or aggravated by, these anticoagulants per 1000 days of anticoagulant therapy.

the drug was stopped promptly, bleeding tended to subside within 24 to 48 hours under both drugs when there was no underlying pathology conducive to bleeding. Although the prothrombin time fell more rapidly after cessation of Tromexan than of dicumarol, the hemorrhages did not always wane proportionately, sometimes persisting for a few days after the prothrombin times had regained low levels. Such continued bleeding was usually minor and not a threat to the patient. Synthetic vitamin K preparations were employed in 34 per cent of the episodes of hemorrhage related to Tromexan and 16 per cent of the episodes related to dicumarol. It appeared beneficial, but, because of differences in dosage, nature of bleeding, and so forth, no comparison of its use between the two drugs seemed justifiable.

It is well known that anticoagulant bleeding parallels the rise of prothrombin time. A substantial increase in incidence was found in the dicumarol study to begin at about 50 seconds (7 per cent) and a larger increase to occur

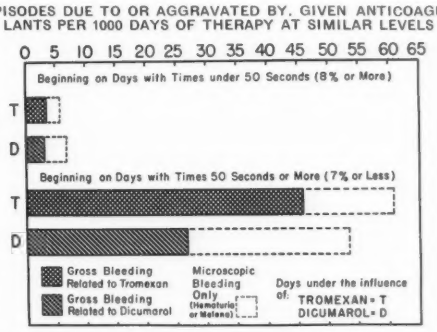
EPISODES DUE TO OR AGGRAVATED BY, GIVEN ANTICOAGULANTS PER 1000 DAYS OF THERAPY AT SIMILAR LEVELS
0 5 10 15 20 25 30 35 40 45 50 55 60 65
Beginning on Days with Times under 50 Seconds (8% or More)
T
D
Beginning on Days with Times 50 Seconds or More (7% or Less)
T
D
Gross Bleeding Related to Tromexan
Gross Bleeding Related to Dicumarol
Microscopic Bleeding Only (Hematuria or Melena)
Days under the influence of: TROMEXAN = T DICUMAROL = D

FIG. 9. Number of bleeding episodes due to, or aggravated by, anticoagulant therapy beginning on days when patients were under the influence of Tromexan or dicumarol and showed times under 50 seconds and 50 seconds or more per 1000 days of anticoagulant therapy characterized by times at similar levels.

above 60 seconds (6 per cent or less).[18] The question arose, therefore, whether the slightly higher rate noted for Tromexan occurred at all prothrombin levels or only at high levels. Figure 9 demonstrates the findings in this regard. The gross hemorrhage rates for Tromexan and dicumarol were nearly identical for prothrombin times below 50 seconds, namely 3.5 episodes related to anticoagulants per 1000 days with known prothrombin times for Tromexan versus a corresponding figure of 3.1 per 1000 for dicumarol. Basically, the incidence of hemorrhage at these levels would appear to be the same for the two drugs. Actually, these are the levels at which most of the bleeding began (that is, 79 per cent of the episodes) but the incidence per 1000 days with such readings shown in figure 9 are low because about 97 per cent of the prothrombin times also fell in this

* Since the recorded duration of a microscopic hemorrhage is greatly influenced by the frequency of laboratory examinations, data on duration are not presented for such hemorrhages. Similarly, duration data for hemorrhages aggravated by anticoagulants are not discussed because it was too difficult to evaluate how many of the total days of such a hemorrhage were due solely to the underlying condition and how many were aggravated by anticoagulants.

range. Although bleeding due solely to anticoagulants occasionally occurred at all levels, bleeding in the presence of underlying pathology showed a tendency to begin at lower levels than bleeding due solely to anticoagulant therapy. Persistent bleeding in this range should instigate an investigation of the possibilities of causes other than anticoagulants (for example, malignancy[20]).

At times above 50 seconds the incidence of bleeding shot up dramatically, as figure 9 indicates. Under Tromexan there were 197 days with recorded times at these levels during which nine gross and three microscopic hemorrhages related to Tromexan began, a rate of 46 gross hemorrhages and 61 total hemorrhages per 1000 days. On the 75 dicumarol days known to have reached 50 seconds or more, two gross and two microscopic hemorrhages related to dicumarol also began, a corresponding rate of 27 gross hemorrhages and 53 total hemorrhages per 1000 days. Because the number of days at these high levels was limited, the difference may be a chance one. On the other hand, this difference may arise from the fact that a somewhat larger proportion of the Tromexan prothrombin times above 50 seconds were excessively high and bleeding would be expected to occur in such zones. These occasional high times, plus the higher proportion of all Tromexan readings in the zone of 50 seconds and above, appear to be the two most reasonable explanations, other than chance, for the higher overall bleeding rate for Tromexan.

A further bit of evidence pointing toward the difficulties in control as the underlying cause of the differential noted is the fact that the differences between the two drugs in rates of gross bleeding was greatest during the first two weeks of the illness (5.9 vs. 3.5), decreased in the third and fourth week (4.0 vs. 3.3), and by the fifth week and later was eliminated (2.6 vs. 2.5).* Although explanation on a chance basis cannot be conclusively ruled out, it seems more reasonable to attribute this decreasing difference to the higher prothrombin times which often occurred early in Tromexan administration before experience with a given patient's particular reaction pattern had been gained. As the times were stabilized, the risk of hemorrhage diminished. With the use of divided daily doses, particularly during the initial weeks, it should be possible to improve substantially on the hemorrhage record herein presented for Tromexan.

* These figures omit both days and hemorrhages in cases for which the date of onset was unknown.

Toxic Reactions

The causal relationship of symptoms to specific drugs, especially when several drugs are being administered simultaneously to ill patients, is extremely difficult to evaluate. The reactions noted below include only those in which there appeared a logical relationship to the anticoagulants.

Tromexan is dispensed in 150 and 300 mg. tablets. The pill, like dicumarol, is slightly bitter to the taste, although not objectionably so. Occasionally it is responsible for mild systemic reactions. The following reactions to Tromexan have been noted by the observers in this study:

Nausea	7	Urticaria	2
Vomiting	2	Maculopapular rash	2
Diarrhea	2	Dyspnea	1

A total of 12 patients, or 4.2 per cent of all patients receiving Tromexan, showed one or more such reactions.

The only reaction clearly related to dicumarol in this series was one episode of nausea and vomiting. (This case constitutes 0.4 per cent of all patients receiving dicumarol.) It is possible that more reactions occurred with dicumarol but were not reported, as less attention would be paid to minor gastrointestinal symptoms occurring with this drug than in the case of Tromexan which was undergoing its first clinical trial in many of these institutions.*

An interesting though incidental observation reported from the Henry Ford Hospital† was the apparent relief of cardiac angina by Tromexan. The patient, a 62 year old male,

* The episode of dyspnea was associated with nausea, vomiting and urticaria following an initial 1500 mg. dose of Tromexan.

† Carefully reviewed by Dr. Lawrence Denham, Resident Cardiologist at that Hospital.

was admitted to the hospital with decubitus angina and "acute coronary insufficiency." It was noted that dicumarol, given prophylactically, exerted no beneficial effect on the angina during his hospital course. Shortly after discharge the patient suffered a myocardial infarction and on rehospitalization was given Tromexan in lieu of dicumarol. For the next three weeks, while the patient was on Tromexan, the pain disappeared. On reinstitution of dicumarol for one week, the pain reappeared, and a switch back to Tromexan resulted in a disappearance of the angina which has not recurred since ambulatory Tromexan therapy. The significance of this is not clear, in view of the psychic factors and vagaries of cardiac angina. Reports of the beneficial effects of dicumarol and heparin on angina have appeared.[22, 23] No previous report exists of similar effects from Tromexan.

Laboratory Evidence of Toxicity

Since previous work had revealed aggravation of hepatorenal disfunction following Tromexan administration,[14] a number of laboratory tests were included in the study. In addition to the routine blood count, urine and stool studies, the following were studied: (1) sedimentation rate, (2) liver function tests (cephalin flocculation, thymol turbidity, albumin-globulin ratio, BSP), (3) renal function tests (phenolsulfonphthalein, nonprotein nitrogen), (4) blood cholesterol. Although these tests were not performed at sufficient intervals to be satisfactory for a precise statistical evaluation of minor changes, no gross evidence of toxicity resulting from the use of Tromexan or dicumarol was found, either in our own review of the individual laboratory results or from the statements of the physicians participating in the study. Rarely a slight rise in nonprotein nitrogen (or urea) has been noted during the use of both drugs, but these have occurred in the presence of renal pathology. The significance of a relationship to anticoagulants has in each instance been doubtful. One patient in serious shock from myocardial infarction developed renal shutdown which coincided with the initial dose of Tromexan. The shock appeared to be an adequate cause for this complication. The administration of either drug in the face of shock and oliguria may result in very rapid and dangerous elevations of the prothrombin time.[24] Figure 10 illustrates this rapid prothrombin response in the setting of renal shutdown and its treatment with vitamin K_1 oxide.[25] Heparin has also produced excessive response when administered in the presence of shock. Even in the presence of severe renal disease no significant alteration in the chemical findings were noted in this series from the administration of Tromexan or dicumarol.

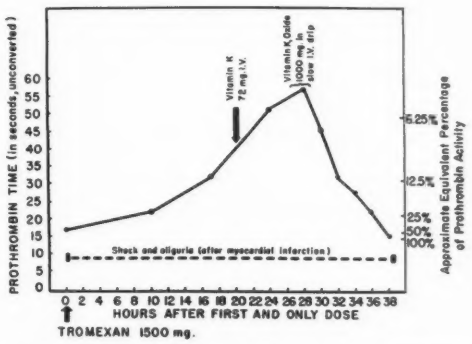

FIG. 10. *Effect of shock on the response to Tromexan.* Excessive response to Tromexan in patient with myocardial infarction and subsequent shock with oliguria. (Excessive hypoprothrombinemia occurred 28 hours after a single 1500 mg. dose of Tromexan. Note lack of effect of water-soluble vitamin K and subsequent rapid response to vitamin K_1 oxide.)

THE EFFECTS OF OTHER DRUGS ON ANTICOAGULANTS

The doses of xanthines, salicylates, penicillin, and adrenocorticotropic hormone used in this study exerted no obvious influence on the prothrombin time following Tromexan or dicumarol. The use of aureomycin and terramycin apparently had a profound effect on the prothrombin response to these drugs, noted in four cases in our series. In one case when aureomycin and terramycin were administered shortly before the anticoagulant, the prothrombin time rose excessively after the usual initial dose of anticoagulant and had an unusually delayed fall (fig. 11). In three cases when the antibiotic was given during the course of anticoagulant therapy, a diminution in the dosage

of the drug was necessitated to keep the prothrombin time within the therapeutic range. Although no study of this relationship has been carried out, it has been suggested that sterilization of the gastrointestinal tract by the antibiotics interferes with the production of vitamin K by intestinal bacteria.[20] Failure to moderate the dosage of coumarin derivatives when these antibiotics are being used may result in dangerous prothrombin times and consequent hemorrhages.

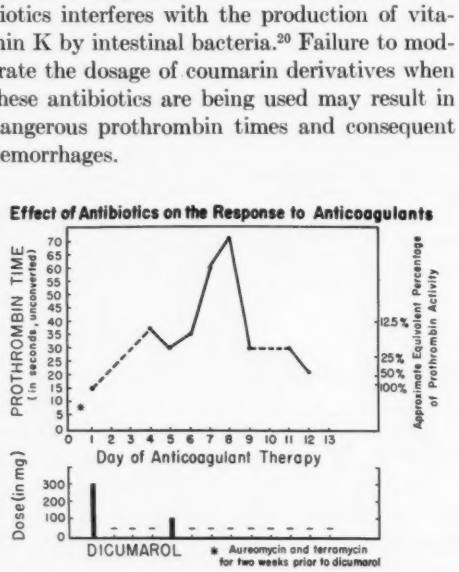

FIG. 11. Case illustrating marked hypoprothrombinemia after small doses of dicumarol. (Patient had taken aureomycin and terramycin for "gastroenteritis." He developed thrombophlebitis of the leg shortly after this had subsided. Note the slow return of the hypoprothrombinemia toward normal. Dotted extensions denote lack of available prothrombin times.)

DEATHS OCCURRING DURING THE STUDY

There were 44 deaths reported in this series of which 42 occurred within six weeks of the date of onset (or hospitalization).* (Eight other deaths reported from the various hospitals were not included as they occurred after the period of study.) Table 2 previously presented shows the breakdown of deaths within the period of observation by the different diagnostic groups. Because of the variety of thromboembolic illnesses, the small numbers in some diagnostic groups, and the varying periods of observation, the data furnish an unsound basis for death rates in a statistical sense, with the possible exception of myocardial infarction.

Deaths among Myocardial Infarction Cases

The counts are too small in most categories to use to compute the percentage dying by diagnostic groups and are unsuitable in other respects for case rates and for comparisons between Tromexan and dicumarol. To enable the reader to identify the type of sample involved, it is reported that omitting deaths after six weeks and in mixed drug cases, 10.8 per cent of the 139 myocardial infarction cases treated with Tromexan are known to have died within six weeks of the time of onset of the attack and 14.2 per cent of the 106 myocardial infarction cases treated with dicumarol.* The difference in deaths under the two anticoagulants may reflect the higher proportion of cases mild at onset in the Tromexan group and other miscellaneous differences in sampling, as well as the operation of chance factors. Also the dicumarol rate is increased slightly by the deaths that occurred coincidentally with Paritol supplementation of dicumarol reported in the subsequent discussion.† Neither of these above percentages may be used justifiably to evaluate the relative merits of the two drugs since the deaths in most cases were related only indirectly, or not at all, to the type of anticoagulant employed. Both percentages are below the experience in the study of dicumarol in myocardial infarction[18] in which deaths within six weeks amounted to 16.0 per cent of the total treated group;‡ close comparison is not warranted because of the difference in the cases sampled and the differences in length of observation and timing and length of anticoagulant therapy.

* Date of hospitalization was used when the date of onset had not been reported and could not be estimated.

* These percentages may understate slightly actual deaths since not all myocardial infarction cases were followed six weeks, but the error should be small since deaths shortly after hospital discharge are usually reported to the hospital or physician concerned.

† When the two deaths in which Paritol may have been implicated are deducted, the percentage of dicumarol cases dying within six weeks becomes 12.3 per cent. (Paritol used in this series was an early lot and no longer in use.)

‡ This rate includes cases denied dicumarol because of medical contraindications. When these are omitted, the rate becomes 15.2 per cent.

Of the 31 deaths in patients with myocardial infarction, 14 died in heart failure, three died of embolic phenomena, three died of extension of the previous infarct or fresh infarction, two died in uremia, one of a ruptured interventricular septum, and one of a ruptured myocardium and hemopericardium (autopsy). In seven patients the cause of death was not ascertained. These latter patients died suddenly during the hospital course and no autopsies were performed. Four of the 31 deaths were related to anticoagulants and will be described in detail. One case of myocardial rupture was reported, and one case of rupture of the interventricular septum. (Both patients were on dicumarol and both episodes occurred on the fourth day of therapy as the prothrombin time was entering the therapeutic range).

Among the coronary group, death due to thromboembolism occurring during anticoagulant therapy was established in only three patients.* These were all due to peripheral emboli, as the deaths caused by extension of a previous infarction or a new infarct (a total of three) occurred in each case after anticoagulants were stopped. One patient, on dicumarol and in the therapeutic range for the previous three days, died shortly after an embolus to the leg. Prior to that the prothrombin time was in the therapeutic range approximately 50 per cent of the time, the remainder being below the therapeutic range. Two other patients died of cerebral emboli following myocardial infarction while on Tromexan. One patient suffered a cerebral embolus the day after a massive infarction and 18 hours after the first dose of Tromexan. The prothrombin time had reached 35 seconds, due to shock and resulting oliguria in this patient. In the other case a cerebral embolus occurred on the eighteenth day following infarction. The prothrombin time was 30.0 seconds on the day of the embolus, but previously the prothrombin time was less than the therapeutic range 80 per cent of the course.

It is of interest that the three myocardial infarction cases who died of extensions or new myocardial infarctions (as shown by definite electrocardiogram changes or by autopsy) developed these after the cessation of anticoagulants. Two patients who had received Tromexan for the initial infarction, one for two weeks and the other for five weeks, developed a recurrence on the third day following the cessation of Tromexan. In the one patient who died of a fresh infarction following dicumarol, the incident occurred on the tenth day after dicumarol was stopped (patient received dicumarol for four weeks).

Deaths in the Noncoronary Group

Of the 13 deaths which occurred in cases other than myocardial infarction, only two were believed to be due to thromboembolic accidents occurring during the period of anticoagulation.* Both of these cases were treated with Tromexan. Both illustrate the occasional failure of anticoagulants to eliminate such risks. One patient in cardiac failure secondary to old rheumatic heart disease with subsequent phlebothrombosis of the right leg developed phlebothrombosis of the left leg while at an adequate prothrombin time and shortly thereafter died of a "probable" pulmonary infarction. The prothrombin times were satisfactory except for two readings slightly below the therapeutic range on the third and fourth day before death.† No autopsy was performed. In the second instance‡ a patient with arteriosclerotic heart disease and a recent pulmonary infarction suffered a second pulmonary embolism eight days after the first with prothrombin activity at about 6 per cent for the previous three days. No reading was obtained on the day of death as the patient died early in the morning. At autopsy a fresh pulmonary embolism was found. Death had occurred so rapidly from this that no infarction had as yet formed.

Autopsy Material

Complete autopsy protocols were received in 14 of the 44 fatalities. Ten of these were cases

* It is possible that some further deaths due to thromboembolism are included among cases dying of unknown causes.

* As before, only cases where the diagnosis of thromboembolic complications appeared rather definite are considered.

† The prothrombin time was not completely adequate for the three-day period.

‡ Not included in section on complications because embolism was diagnosed at autopsy, not clinically.

of myocardial infarction, three of pulmonary embolism, and one of multiple cerebral emboli of unknown origin. In the myocardial infarction group six cases received Tromexan and five received dicumarol (two Tromexan cases and one dicumarol case also received heparin initially). While the smallness of the group prohibits any statistical appraisal, certain facets of the autopsy reports are of interest. The protocols were examined for evidences of mural thrombi subsequent to the infarction, and in those cases where such thrombi were present, for the relation of these to the anticoagulant control. Of these 10 myocardial infarction cases, nine cases failed to demonstrate any intracardiac thrombi. In these nine cases the prothrombin control was considered reasonably adequate in that the prothrombin time was in the therapeutic zone approximately 75 per cent of the total anticoagulant period, and particularly during the first week when the incidence of embolic phenomena is at the highest.* That these patients were adequately maintained on anticoagulants was further evidenced by the following: out of a total of 119 prothrombin determinations in these nine cases, only 33 were considered below the therapeutic range (27 per cent of the total) and very few of these occurred on successive days, where the possibility of thrombotic phenomena is greater than when these low times were sporadic as was the case here.

In the one myocardial infarction case that demonstrated a superimposed mural thrombus the patient had been on Tromexan. Because of the uncertain date of the infarction, it was not possible to determine whether this developed in the face of adequate anticoagulant therapy.

Among the four autopsies performed in the nonmyocardial infarction cases, there was one instance of a demonstrable clot formation under anticoagulant therapy. This was described above as the pulmonary embolus occurring under apparently adequate Tromexan therapy.

Because of the small amount of autopsy material, no definite conclusions concerning the relative prophylactic powers of the two drugs can be drawn. In the myocardial infarction group the extremely low incidence of mural thrombi conforms with the former observations that adequate anticoagulants diminish the incidence of this complication. The isolated pulmonary infarction episode must be considered a pure anticoagulant failure.

Possible Anticoagulant Deaths

Deaths related to anticoagulant hemorrhage are a major concern during such therapy. This toxic effect of anticoagulants appeared intimately connected with the death of four patients in this series. In two of these the combined use of Paritol (a heparin-like synthetic polysaccharide) and dicumarol were thought to have participated in the deaths by causing cerebral hemorrhages. Both patients had elevated clotting time (due to Paritol) in the face of massive myocardial infarction with hypotension and oliguria. In the first patient the prothrombin time was 54 seconds (not converted)* before death and an ecchymotic rash appeared over the face and thighs prior to death. It was the clinical impression of the attending physician that Paritol† and possibly dicumarol contributed to death in this case. The other patient on dicumarol plus Paritol expired 24 hours after admission with a clotting time of 160 minutes and a prothrombin time of 22 seconds. The possibility of cerebral hemorrhage was also considered in this case. Autopsies were not performed in either case. Because of the concomitant use of Paritol, the role of dicumarol cannot be assayed in these cases.

Tromexan appeared to be a cause of death through hemorrhage in two patients. They are herewith described in detail. A 44 year old male was admitted to the hospital for observation of vague upper abdominal pain. He had rheumatic heart disease and was fibrillating. On his thirteenth hospital day a cerebral accident occurred. This was thought to be a cerebral embolus and Tromexan was administered. He received 1500 mg. the first day, then suc-

* In the original dicumarol study[18] mural thrombi were found in 32 per cent of the cases treated with dicumarol and examined at autopsy and in 63 per cent of the control cases that had received no anticoagulant therapy.

* The clotting times were not available.

† The Paritol used in this study was an early experimental lot.

cessively 1200, 600 and 900 mg. over the following three days (fig. 12). On the fifth day after starting Tromexan the prothrombin time was 140 seconds (2 per cent) and the drug was stopped. On the following day gross hematuria appeared. The prothrombin time fell slowly and four days later was still 69 seconds (7 per cent). On this day nuchal rigidity appeared and a diagnosis of subarachnoid hemorrhage was made. Large doses of vitamin K were given and the prothrombin time fell to 25 seconds the following day. However, the patient expired in a few days. A post-mortem exami-

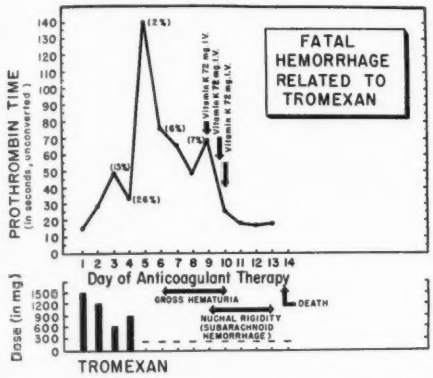

FIG. 12. Case of subarachnoid hemorrhage during Tromexan therapy with fatal outcome.

nation revealed the following: mitral stenosis without auricular thrombi, numerous old and recent renal infarcts, focal hemorrhages in the lungs, a diffuse subarachnoid hemorrhage with no evidence of local arterial or venous pathology. No embolus was demonstrated.*

A 65 year old female with arteriosclerotic and hypertensive heart disease was admitted to the hospital in acute pulmonary edema. She was put on Tromexan because of a suspected myocardial infarction. (Left bundle branch block was present.) Her progress was considered fair, but on the tenth hospital day she expired suddenly. She had been in the therapeutic range throughout her course on a daily dose of 900 or 1200 mg. of Tromexan. Her prothrombin level was 12 per cent on the day of death. An autopsy revealed an old healed myocardial infarction (over four months) and a healing infarction of one to two months duration. Striking features were the large areas of hemorrhage throughout the healed infarct, also hemorrhages in the right upper and right lower lobes of the lung, and in the spleen. The cranial cavity was not explored. There was no known bleeding tendency. The immediate cause of death was considered to be probably heart block but multiple hemorrhages and the possibility of intracranial hemorrhage were not ruled out.

Among the other thromboembolic groups, one other patient died of a subarachnoid hemorrhage. This patient, a 58 year old male, a cerebral spastic with quadriplegia, was given Tromexan because of a thrombophlebitis of the left leg. After two weeks of Tromexan, during which time his prothrombin time did not exceed the therapeutic range, the drug was discontinued. Five days later, when the prothrombin time had fallen to 19.2 seconds he suffered a spontaneous subarachnoid hemorrhage and expired.

The possibility that Tromexan was a lethal factor in two of the above cases appears likely. In the dicumarol cases, the simultaneous use of Paritol renders it difficult to evaluate the role of dicumarol. In the first Tromexan case hemorrhage seems related to the marked prolongation of the prothrombin time.* In the second patient the cause of the extensive bleeding without unusual prolongation of the prothrombin time is not clear and an undiagnosed hemorrhagic diathesis may have been present, potentiating the effects of Tromexan. In the

* It is therefore at least possible that the original cerebral accident was a hemorrhage prior to the use of any anticoagulant and that the Tromexan aggravated this. This case illustrates (a) the need for very careful diagnosis of cerebral lesions before the administration of anticoagulants and (b) the need for more careful control of the administration of anticoagulants.

* This case is instructive in illustrating the pitfalls of anticoagulant therapy (fig. 12). Administration of a larger dose of Tromexan in the presence of an elevated prothrombin time (fourth day) resulted in a more serious prolongation of the time. The hematuria occurring at such elevated times merited more rigorous antidotal therapy (vitamin K_1, blood, etc.) as these persistent high elevations in the prothrombin time are a real hazard to a patient.

third patient the occurrence of hemorrhage with a prothrombin time that was practically normal suggests the relationship to Tromexan is fortuitous. Such instances serve as a dramatic re-emphasis that anticoagulant therapy warrants constant meticulous attention. Dicumarol has recently been reported as a leading cause of death due to drugs.[25] Many of these fatalities were due to faulty use of this drug and therefore should be preventable in the future.

Summary and Conclusions

This study was designed to evaluate the relative merits of Tromexan and dicumarol for anticoagulant therapy. A total of 514 patients with actual or threatened thromboembolic conditions were treated with one or both of these anticoagulants. A total experience of 6,642 days of Tromexan therapy and 5,006 days of dicumarol therapy without supplementation with other anticoagulants was reviewed and analyzed. Responsible investigators from seven hospitals cooperated in the project by reporting each individual case on a detailed master form to the Central Laboratory. Analysis of findings from these cases has resulted in the following conclusions as to the relative advantages of the two anticoagulants:

1. Previous reports that a more rapid initial prolongation of prothrombin times can usually be achieved with Tromexan than with dicumarol have been confirmed. This characteristic makes it possible to protect the patient more rapidly with Tromexan than with dicumarol in the initial stages of anticoagulant therapy when the risk of thromboembolic complications is usually especially high, as well as after a lapse in therapy when a rapid return to therapeutic levels is indicated.

2. Previous reports that prothrombin times usually return more rapidly to normal after the cessation of Tromexan than after cessation of dicumarol have been confirmed in a variety of circumstances. This characteristic of Tromexan is of advantage when it becomes advisable to terminate therapy, as when excessively prolonged times, with or without bleeding, develop or when emergency surgery becomes necessary.

3. The power of the two anticoagulants to protect the patient from thromboembolic complications appeared about equal, as demonstrated by the close similarity in the thromboembolic complication rates for days of therapy under each of the two anticoagulants.

4. More of the thromboembolic complications under Tromexan occurred when prothrombin times were below the optimal therapeutic range than did those under dicumarol. This suggests that control of the lower limits of the therapeutic range presents more of a problem with Tromexan than with dicumarol.

5. Mild toxic reactions (nausea, diarrhea or rashes) were infrequent, being reported in 12 (4.2 per cent) of the patients treated with Tromexan and in one (0.4 per cent) of the patients treated with dicumarol. These reactions did not constitute a significant disadvantage in the use of either drug.

6. A review of the laboratory test findings for all patients failed to reveal any evidence that either Tromexan or dicumarol produced significant evidence of toxicity in the doses commonly used for therapy.

7. Fourteen autopsies were studied in detail. These did not reveal any difference in the toxicity of the two anticoagulants or in their effectiveness in preventing thromboembolic complications.

8. A higher proportion of total prothrombin times were 50 seconds or more (7 per cent or less) during Tromexan therapy than during dicumarol therapy. These were mostly encountered in patients on a single daily dose.

9. This tendency to excessive response was reduced markedly in those patients who received Tromexan in divided daily doses.

10. The total rate of gross hemorrhage related to anticoagulants was slightly higher during Tromexan therapy than during dicumarol therapy. This difference was found primarily at times of 50 seconds or over and during the early stages of anticoagulant therapy.

11. When observations were limited to days when prothrombin times were under 50 seconds (above 7 per cent), the incidence of hemorrhagic episodes due to, or aggravated by, the two anticoagulants appeared approximately similar, indicating that the observed differences

in total hemorrhage rates (see item 10) were related to the more frequent upward fluctuations under Tromexan under single daily doses and not to some other inherent characteristic of this anticoagulant.

12. These combined observations (items 8 to 12) suggest that, when given in single daily doses, Tromexan is slightly more difficult to control than dicumarol. Experience with the daily total divided into two or three doses indicates that the prothrombin time is more satisfactorily controlled with this regimen than with single doses.

13. In this series of patients two deaths occurred in which Tromexan was probably implicated. In one of these, poor control of prothrombin times played a role. Two deaths occurred in patients who were on the combination of Paritol and dicumarol therapy. The clotting times were prolonged in both and the prothrombin times were 54 and 22 seconds respectively. It is difficult to assay the part played in these deaths by each of the two anticoagulants involved.

14. As with all coumarin derivatives and phenylindanedione, the prothrombin times of patients receiving Tromexan should be watched with especial care until the response pattern is fully evident. Thereafter the use of anticoagulants requires meticulous supervision by the attending physician.

15. The foregoing conclusions relate to the total experience with Tromexan and dicumarol when employed in a variety of thromboembolic conditions in the present study. In addition, some comparisons are possible with the findings of the previous study of the use of dicumarol in myocardial infarction.[18] Such comparisons require, however, the omission from the present study of patients with diagnoses other than myocardial infarction. These omissions reduce the sample to 262 patients, of whom 139 received Tromexan only; 106, dicumarol only; and 17, both anticoagulants. The following conclusions pertain only to this component of the total sample:

(a) Of the myocardial infarction patients receiving dicumarol only, 14.2 per cent died within six weeks of the date of onset as compared with 10.8 per cent of the patients receiving Tromexan only. Since two of the dicumarol deaths occurred in association with the combined use of Paritol and dicumarol, and since slightly more of the Tromexan cases were mild at onset, and for other reasons, these differences cannot be attributed to differences between the two anticoagulants. Both death rates are slightly below the 16.0 per cent record of deaths within six weeks in the treated group in the previous dicumarol study and very substantially below the 23.4 per cent of deaths occurring in the control group in that study.

(b) The thromboembolic complication rates for the myocardial infarction patients were similarly favorable when compared with the results of the previous dicumarol study. During Tromexan therapy in the present study, thromboembolic complications averaged 2.3 per 1000 days of therapy and during dicumarol therapy, 2.2 per 1000 days. These day rates are both about one third lower than the corresponding rate of 3.1 complications per 1000 days during the period of dicumarol therapy in the previous study and significantly below the 12.6 rate per 1000 days for the control group in that study during days of their illness corresponding to the period of therapy for the treated group.

(c) Thus the power of protection of the two anticoagulants in myocardial infarction does not vary greatly. When judged by comparison with the control group of the previous study, both produced significant reductions in death rates and in the incidence of thromboembolic complications. The experience of this study with an additional 262 patients with myocardial infarction therefore constitutes further confirmation of the major conclusions of the original study.

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Clinical Use of the Anticoagulant Phenylindanedione

Report of 74 Cases

By Frederick W. Preston, M.D., Wm. R. O'Connor, M.D., Charles E. Thompson, M.D., and Eldis N. Christensen, M.D.

Phenylindanedione is an anticoagulant similar in action to the coumarin series of compounds. Like dicumarol, it is effective orally, acts by lowering blood prothrombin content, and its administration is controlled by daily blood prothrombin determinations. A study of the effective dosage, rapidity of action, cumulative effect and hemorrhagic complications produced by this drug shows that it is a practical anticoagulant for clinical use and has certain advantages over dicumarol.

THE ANTIPROTHROMBIN effect of certain indanediones when administered orally to animals was first investigated by Kabat, Stohlman and Smith.[8] Phenylindanedione, an additional derivative, was studied by Meunier, Mentzer and Molho,[10] Soulier and Gueguen,[16] and Jaques, Taylor and Lepp[7] who reported that it is of a low order of toxicity, is a quicker acting prothrombinopenic agent than dicumarol, and that the effect from a single dose is of shorter duration. Bjerkelund[2] demonstrated that phenylindanedione has no effect on the concentration of factor V (Owren) and that vitamin K in large doses intravenously has an antagonistic effect on its prothrombin reducing action. It was first used clinically as an anticoagulant by Soulier and Gueguen[15] and by Blaustein, Croce, Alberian and Richey.[4] The purpose of this paper is to report our experiences in the clinical use of this anticoagulant.

Cases Studied

Seventy-four hospitalized patients were studied. The initial diagnosis in 65 who had thromboembolic episodes before anticoagulant therapy was started was acute coronary thrombosis in 44, thrombophlebitis in 20 and pulmonary embolism in one. Eight patients were given the drug on a prophylactic basis. Four of these had coronary insufficiency and four had congestive heart failure. In addition, a patient with acute pericarditis was treated. Of the cases with thrombophlebitis 17 occurred spontaneously before the patients were admitted to the hospital and four occurred postoperatively. Among the patients with acute myocardial infarction there was one who developed peripheral thrombophlebitis before anticoagulant therapy was started.

Dosage

Initial dosage varied from 75 to 200 mg. given as soon as possible after the diagnosis was made regardless of the time of day. On subsequent days the drug was usually administered twice daily in dosages of 50 mg. Total dosage in 74 patients varied from 350 to 11,040 mg. given over periods of time varying from 5 to 102 days. The average total dose was 2255 mg. and the average duration of treatment was 23 days. The drug was administered orally in tablet form, each tablet containing 50 mg.

Control of Blood Prothrombin

Blood prothrombin determinations were done before anticoagulant therapy was started and daily thereafter until several days after therapy was discontinued or until the blood prothrombin activity had returned to normal. The one stage method of Quick[14] was used, employing a commercial thromboplastin prepared from acetone-dried rabbit brain

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Phenylindanedione for this study was supplied by the Abbott Laboratories, North Chicago, Ill.

which gave a prothrombin time of 13 seconds in normal patients.* Saline suspensions were made freshly each day from dehydrated thromboplastin supplied in ampules. For recalcification 0.02 molar calcium chloride was used. Results were expressed in terms of per cent of normal prothrombin activity. For this thromboplastin a clotting time of 13 seconds represented a prothrombin concentration of 100 per cent and 33 seconds a concentration of 12.5 per cent of normal.

Errors in blood prothrombin determination were kept at a minimum throughout this study by (1) use of thromboplastin with constant activity, (2) daily assays of thromboplastin against normal blood to determine its potency, and (3) experienced technicians (two technicians did over 85 per cent of the

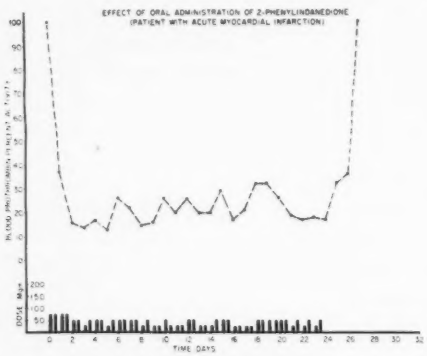

FIG. 1.

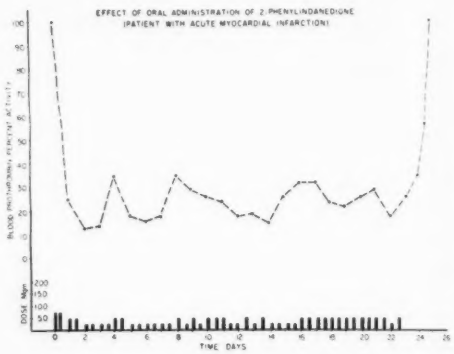

FIG. 2.

determinations). In addition, care was taken not to allow blood drawn for prothrombin assays to stand at room temperature for more than one hour before the determination was made. Quick has emphasized the importance of these factors in securing accurate results.[14]

RESULTS

Figure 1 illustrates the effect of phenylindanedione on a patient in whom an adequate level of prothrombin depletion was maintained with a dose averaging 85 mg. daily. The rapid fall of blood prothrombin content within the first 24 hours is typical of the action of this drug, as is the return of prothrombin to normal levels within three days after the final dose. Figure 2 illustrates the effect of the drug in a patient in whom control was not quite as satisfactory as the first.

In spite of an attempt to keep blood prothrombin levels between 10 and 30 per cent of normal, there was difficulty in maintaining this deficiency in many instances. In three patients prothrombin activity remained consistently above the therapeutic range in spite of daily doses averaging 109, 118, and 121 mg. respectively, which was greater than the average dose given the remaining patients. These were the only instances of resistance to the drug, and it is probable that satisfactory prothrombin deficiency could have been produced in these patients by increasing the dose. In the remaining 71 patients after the blood prothrombin content had been depressed to the desired level 65 per cent of subsequent daily determinations fell within the 10 to 30 per cent range until the drug was discontinued. In three patients the prothrombin was below 10 per cent of normal activity for at least two consecutive days, and in one instance it was thought necessary to correct the deficiency by the administration of whole blood and vitamin K intravenously. In 31 patients the prothrombin activity rose to above 30 per cent for at least three consecutive days, and in 29 patients there was an escape to over 50 per cent of normal on at least one occasion.

Administration of the drug to these patients was in most cases done by resident physicians who determined the dose each day from the patient's prothrombin determination of 9 a.m. In general with more experience better control of prothrombin levels is obtained, and it is probable that the control in these patients is

*Manufactured by Cappel Laboratories, Wayne, Pa.

similar to what would be obtained by most physicians interested in using this anticoagulant.

The average daily dose required for maintenance of prothrombin deficiency was increased by dividing the dose, 79 mg. daily for 22 patients who received the drug once daily and 102 mg. for 43 patients who received it twice daily.

Age did not seem to affect the dose requirement appreciably. The amount required to maintain satisfactory prothrombin depletion in patients who received the drug twice daily averaged 103 mg. daily for 10 patients under 50 years of age, 96 mg. for 21 patients 50 to 60 years of age and, 100 mg. for 19 patients over 60 years of age.

One patient with acute myocardial infarction had a fresh infarction proved at necropsy while on anticoagulant therapy. A second patient had multiple pulmonary infarcts verified at necropsy, some of which may have occurred during the time of therapeutic prothrombin deficiency. No other episodes of fresh thrombosis or embolism were observed in any patient while under therapy with phenylindanedione.

The mortality in 44 patients with myocardial infarction was 13.3 per cent. Although this mortality compares favorably with reported series treated with dicumarol[9, 12, 13] the number of cases is not large enough to be significant. It is planned to make these patients the subject of a separate report when a sufficient number of cases is added.

Toxic Manifestations

Soulier and Gueguen[15] using doses three to four times as large as ours reported mild reactions consisting of polyuria, polydipsia and tachycardia in some patients. However, in our series no toxic effects other than hemorrhagic phenomena were observed.

Gross hematuria occurred in one patient whose prothrombin concentration had dropped to less than 6 per cent of normal. It was not definite that the hematuria was related to the anticoagulant because an indwelling catheter was in place; however, the hematuria subsided when the prothrombin was allowed to resume a higher level.

Routine urinalyses were done during the course of therapy in 34 patients at approximately weekly intervals. Transient microhematuria occurred in two (5.9 per cent) when prothrombin concentrations were 8 per cent and 15 per cent respectively. In both patients, the hematuria promptly cleared when the anticoagulant was omitted and the prothrombin concentrations were allowed to resume slightly higher levels.

A hemorrhage of about 250 cc. occurred from a paracentesis site in a patient with thrombophlebitis and hepatic insufficiency at a time when his prothrombin activity was 5 per cent. This hemorrhage was not severe, and it was not definitely attributable to the anticoagulant.

Petechiae involving both lower extremities occurred in one patient on the third day of therapy when the prothrombin was 15 per cent of normal activity. These gradually cleared after the prothrombin was allowed to return to 36 per cent but reappeared on one other occasion during the ensuing 35 days of anticoagulant therapy. Both episodes occurred during quinidine administration.

Prolonged Therapy

Ten patients received the drug for periods of time varying from 33 to 102 days (average 49 days). Total doses received by this group varied from 4125 mg. to 11,040 mg. (average 5687 mg.) None developed an altered tolerance for the drug, and no toxic effects were apparent in these patients.

One of these patients died at home six days after his discharge from the hospital and seven days after his last dose of phenylindanedione. Total dose for this patient had been 5125 mg. during a 41 day period. Necropsy showed that the cause of death was a fresh myocardial infarction. Gross and microscopic examination of the heart, liver, kidneys, spleen, adrenals, gastrointestinal tract and pancreas revealed no toxic effects attributable to the anticoagulant.

Discussion

Interest in phenylindanedione and other dicumarol substitutes has been stimulated by

reports emphasizing that the use of dicumarol has led to serious hemorrhagic complications in some patients. Major hemorrhage occurred in 1.9 per cent of 9,609 patients given dicumarol according to a review of the literature,[1] and in 2 per cent of 15,500 patients treated with dicumarol and heparin by 136 physicians according to a questionnaire.[11] Wright and Rothman[17] have recently reported four cases of fatal hemorrhage following dicumarol administration and summarized 32 other cases from the literature.

It is known that phenylindanedione produces a hemorrhagic diathesis in animals similar to dicumarol if its administration is continued.[6] Whether it will prove to be a safer anticoagulant in humans remains to be seen. No serious hemorrhagic complications have so far been observed in approximately 200 cases previously reported in the literature.[3, 4, 15] The fact that no serious hemorrhages occurred in our patients may be attributable in part to our previous experience with anticoagulants especially dicumarol.

Phenylindanedione has two definite advantages over dicumarol, more rapid action and less cumulative effect. Therapeutic levels of prothrombin deficiency are usually achieved 18 to 36 hours after the initial dose of phenylindanedione, compared with 48 to 72 hours with dicumarol. For rapid anticoagulant effect one must use heparin in conjunction with these drugs. This may be necessary for the first two or three days of anticoagulant therapy with dicumarol but is rarely necessary for more than one day with phenylindanedione.

The effect of phenylindanedione on the prothrombin time usually persists for two to four days after the final dose, as compared to three to seven days after the final dose of dicumarol. This more transient effect of phenylindanedione is particularly advantageous if hemorrhagic complications or other reasons for interrupting anticoagulant therapy occur.

Conclusions

1. Phenylindanedione was used to maintain prothrombin deficiency in 74 patients with thromboembolic disease for periods varying from 5 to 105 days.

2. The recommended initial dose is 150 to 200 mg. A maintenance dose of 50 mg. twice daily will usually maintain blood prothrombin levels between 10 and 30 per cent of normal activity.

3. The desired prothrombin deficiency was usually present 24 hours after the initial dose, and, after the last dose, prothrombin concentration returned to normal in 48 to 96 hours.

4. Resistant patients are infrequent and no patients developed an altered tolerance for the drug while undergoing therapy.

5. Hemorrhagic complications (including microhematuria) occurred in five patients (6.8 per cent) but none were of major significance.

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An Evaluation of the Ability of Priscoline, Regitine, and Roniacol to Overcome Vasospasm in Normal Man

Estimation of the Probable Clinical Efficacy of these Drugs in Vasospastic Peripheral Vascular Disease

By HAROLD D. GREEN, M.D., W. KENNETH GOBEL, MICHAEL J. MOORE, M.D., AND THOMAS C. PRINCE, M.D.

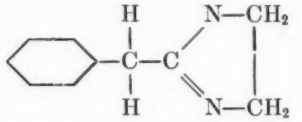
This paper is a study of the comparative efficacy of Priscoline, Regitine, and Roniacol in relaxing vasospasm in the extremities of normal human subjects. A total of 60 studies were performed on 14 subjects. Severe cutaneous vasospasm was induced by exposure of the lightly clad subject to an environmental temperature of 20 C. for one hour or more. In half the tests the severe vasospasm was reduced to moderate vasospasm by application of heat to the torso of the chilled subjects. The effectiveness of the drugs was tested by giving them by intravenous infusion after the appropriate state of vasospasm had been obtained. The degree of relaxation of vasospasm was estimated from the resulting changes in cutaneous temperature recorded with thermocouples.

IN EACH of the peripheral vascular disease entities, the vasomotor component varies. Thromboangiitis obliterans exhibits a decreasing vasospastic element as the organic occlusive element increases.[1] In Raynaud's phenomenon and allied conditions, however, the vasospastic element predominates.[2] Some vasoconstriction is often present in arteriosclerosis. The usage of drugs which abolish vasospasm is, therefore, a helpful adjunct in determination of the degree of vasospasm, in differentiation of the disease entities, and in the treatment of disease where vasoconstriction plays a part in the presenting symptoms.

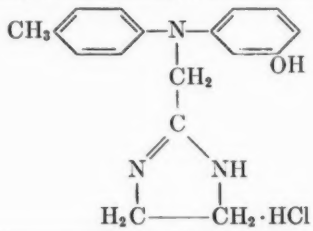
In previous papers usage of such agents in the evaluation of the degree of vasospasm has been discussed.[3, 4] This paper presents a method for estimating the probable clinical effectiveness of drugs designed to relax vasospasm. In principle, a reproducible degree of vasospasm is induced in normal subjects and the ability of the drug to overcome this vasospasm is tested.

The ideal therapeutic agent for this disease group would be one which induced maximal vasodilation in the extremities with minimal untoward side effects. In this paper we will consider three agents and compare the results of their trial upon normal subjects. These agents are: (1) Priscoline,* (2) Regitine,* (3) Roniacol.† The chemical formulas for these drugs are:

Priscoline, 2-benzyl-4,5-imidazoline HCl[5, 6]



Regitine (C-7337) 2-[N-p'-tolyl-N-(m'-hydroxyphenyl)-aminomethyl]-imidazoline[7, 8]



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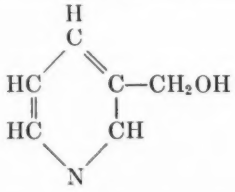
* Kindly supplied by Ciba Pharmaceuticals, Inc., Summit, N. J.

† Kindly supplied by Hoffmann-La Roche, Nutley, N. J.

Roniacol (NU-2121) β-pyridyl-carbinol[9]



Regitine, like Priscoline, has slight inherent vasodilator effect but possesses the ability to convert the normal epinephrine vasoconstriction into vasodilation. When given intra-arterially in a dog, approximately 0.15 mg. per kilogram of Regitine is necessary to completely reverse the action of 1 μg. of epinephrine given intra-arterially. Under similar conditions, 2 mg. per kilogram of Priscoline are required to reverse the action of 1 μg. of epinephrine.

Methods

The method of recording the cutaneous temperature is discussed in more detail, both in validity and mechanics of the method, in previous papers.[1, 2] In all cases, skin temperature was recorded with thermocouples held firmly in contact with the skin by a strip of adhesive, placed about 0.5 cm. proximal to the tip of the couple. In the earlier portion of this study, the skin temperature was recorded on an 8-point Leeds and Northrup Micromax using iron constantin thermocouples (recording time, one minute per point). In the latter portion of the experiment we used a 12-point Brown potentiometer with copper constantin thermocouples (recording time 12 seconds per point).

The subjects were placed in a recumbent position during the study, clad only in undershorts or slips, in a room the temperature of which was kept at approximately 20 C. Individual varients from this temperature are noted in table 1. The temperatures were procured from the right and left third and fourth fingers in the series without body warming, from the index and fourth fingers of the right and left hand in the series with body warming. The lower extremity leads were from the right and left great, middle, and small toes, in both series. Minimal blood flow due to maximal vasoconstriction was considered to be present when the skin temperature approximated the room temperature, and maximal blood flow due to maximal vasodilation when the skin temperature approximated the forehead temperature. Table 1 shows the range of individual forehead temperatures during the respective periods of drug administration. A strong vasoconstriction in the lower extremities and a moderate vasoconstriction in the upper extremities was induced by an initial one to one and a half hour exposure in the constant temperature room. This is illustrated in figures 1 and 2 in the control period prior to the drug infusion, or heating, respectively.

Two methods were followed in the evaluation of the three drugs. These were: (1) administration of the drugs without body warming, (2) administration of the drugs during a period of body warming. The subjects were normal medical students. Ten students received each of three drugs in the first series without body warming. The second study used six of the original subjects and four new individuals; these 10 students were subjects to all three drugs in the body warming series. Each student had his temperature taken previous to the study, and was excluded if febrile. The students did not eat during nor for four hours prior to the experiment.

1. After approximately an hour of body cooling, the ten subjects received either Priscoline, Regitine, or Roniacol. In each case the agent was dissolved in 200 ml. of 0.9 per cent saline and administered by infusion over a period of approximately one half hour. Arterial pressure was checked every five minutes during the infusion and until it stabilized after completion of the infusion. The drugs were given in the following dosage: Regitine 0.5 mg. per kilogram, Priscoline 2.0 mg. per kilogram, and Roniacol 3 mg. per kilogram. Following completion of the infusion the student was retained for at least a half hour recording period; in event of suggestion of further changes the temperatures were recorded until the majority of readings were stabilized.

2. Ten subjects received a combination of body warming plus Priscoline, Regitine or Roniacol, in the above dosages. The period of body warming was preceded by a period of cooling until the temperatures of the extremities approximated room temperature. The body warming was accomplished by heating pads, placed in contact with the back and front of the chests, with one wool blanket covering the torso, and with the extremities exposed. The duration of body warming prior to the drug administration averaged 45 minutes. An effort was maintained to reach maximal vasodilatation by heating, regardless of the duration. At the completion of this body warming period, the infusion was instituted while maintaining warming of the body. Temperatures were recorded until the majority of leads stabilized.

Results

1. *Effects of Drugs without Body Warming.* Paired points on the left and right extremities never differed more than 1 C. The data presented is all for the left extremities. It had been noted in previous studies that the tips of the digits and toes demonstrated the most marked vasomotor changes.[3] The finger, great

and small toes were chosen, therefore, to represent the thermal responses to the drugs. Figure 1 demonstrates the response of 10 individuals to Priscoline, Regitine, and Roniacol without body warming. The range of the room and forehead temperatures during each study, and the month of the year of the study is presented under the appropriate heading in table 1, part A. In the figure, line 1 represents mean room temperature, line 2 represents mean forehead temperature.

a. *Priscoline.* The range of control temperatures and the temperature responses of the fingers and toes is shown in the first three graphs, figure 1. Table 2, column A, gives the average of the control temperatures and the responses of the fingers and toes in the 10 subjects. The average control temperatures demonstrated that a fairly considerable degree of vasoconstriction is present in the toes and a moderate vasoconstriction in the hands. In 7 of the 10 subjects the temperature rose in the fingers and in one it fell subsequent to the drug administration. The temperature in the great

TABLE 1.—*Chart of Range of Room and Forehead Temperatures in Degrees Centigrade of Subjects Used in Figures 1 and 2*

Subject	Legend	Priscoline			Regitine			Roniacol		
		Date	Room Temp.	Forehead Temp.	Date	Room Temp.	Forehead Temp.	Date	Room Temp.	Forehead Temp.
A. Marked vasospasm, figure 1										
AC	A	4	19.5–20.5	30.0–31.5	10	19.5–21.0	26.5–32.0	5	20.0–21.0	31.0–32.0
MP	B	11	20.0	29.5–31.0	11	20.0	30.5–31.5	11	20.0	29.0–30.0
GB	C	4	20.0–20.5	27.0–33.0	10	19.0–20.0	31.0–32.0	5	19.0–20.0	29.5–31.0
KB	D	4	19.5–20.0	32.0–33.0	10	19.0–21.0	30.5–32.0	5	20.0–20.5	30.0–32.0
FW	E	4	19.0–20.0	30.5–32.0	11	20.0	32.0–33.0	5	20.0–20.5	23.5–28.5
EP	F	4	19.5–20.5	31.5–33.0	10	19.5–21.0	30.0–32.0	5	19.5–20.5	31.0–32.0
BG	G	4	20.0–21.5	30.5–32.0	10	20.0–21.5	30.5–32.0	5	19.5–20.0	30.5–32.0
KG	H	5	20.0–22.0	30.5–32.0	10	19.5–20.0	28.0–33.0	5	20.0–20.5	30.0–32.0
JS	I	5	20.0–21.0	30.0–32.0	10	19.0–21.0	31.0–33.0	5	20.0–21.0	—
AS	J	11	20.0	30.0–31.5	11	20.0–21.0	31.5–33.0	11	20.0	32.0
Mean			20.2	31.1		20.1	31.2		20.1	30.4
B. Moderate vasospasm, figure 2										
IM	A	5	19.5–20.0	29.0–32.0	2	21.0–21.5	30.0–33.0	10	20.0	30.0–34.0
RD	B	5	21.0–22.0	30.0–33.0	2	20.0	30.5–32.0	10	19.5–20.0	29.0–31.5
KB*	C	11	21.0–21.5	34.0–34.5	10	21.5	32.5–33.5	11	21.0–22.5	31.5–32.0
KG*	D	11	21.0–22.0	30.5–32.0	11	20.0–22.0	30.0–32.5	11	20.0–21.5	29.5–30.0
JH	E	11	20.5	29.5–33.0	11	20.0	31.0–33.0	10	20.0	28.0–31.5
AC*	F	11	19.0–20.0	30.0–32.5	5	19.5–20.0	28.5–32.0	11	19.0–20.0	29.5–31.0
MP*	G	5	20.0	32.0–34.5	5	19.0–20.0	26.5–30.0	11	20.0	29.0–32.5
AS*	H	3	19.5–20.0	26.0–33.0	12	20.5–21.0	32.0–35.5	10	19.5–20.5	33.0–34.0
JK	I	11	20.5–21.5	28.5–29.5	10	19.5–21.5	22.0–33.0	11	20.0–20.5	30.0–33.0
GB*	J	11	20.5–22.0	29.0–32.5	11	21.0–22.0	30.5–31.0	11	20.0	29.5–30.5
Mean			20.6	31.1		20.6	30.9		20.2	30.9

Part A. Subjects are identified on figure 1 by symbols A to J. The same subjects are used in all 3 studies.

Part B. Subjects are identified on figure 2 by symbols A to J. Six of the subjects in this series are from previous series without body warming (*). Four new subjects were used. All 10 subjects are used in all three studies.

Date column denotes month each individual study was run. *Room* column denotes the range of room temperature during each study, mean is given at the end of each column for that particular column.

Forehead column denotes the range of forehead temperatures of each study, mean also is given at the bottom of the column.

toe rose in six subjects and remained unchanged in four. An increased temperature in the little toe was noted in seven subjects, the temperature remained unchanged in three. This drug caused moderate vasodilation in the fingers and toes. This moderate response is slight feeling of giddiness for a short period subsequent to the experiment.

b. *Regitine.* Regitine, second row of figure 1, exhibits essentially the same picture as Priscoline. The maximal temperatures reached, after giving the drug, are slightly less than

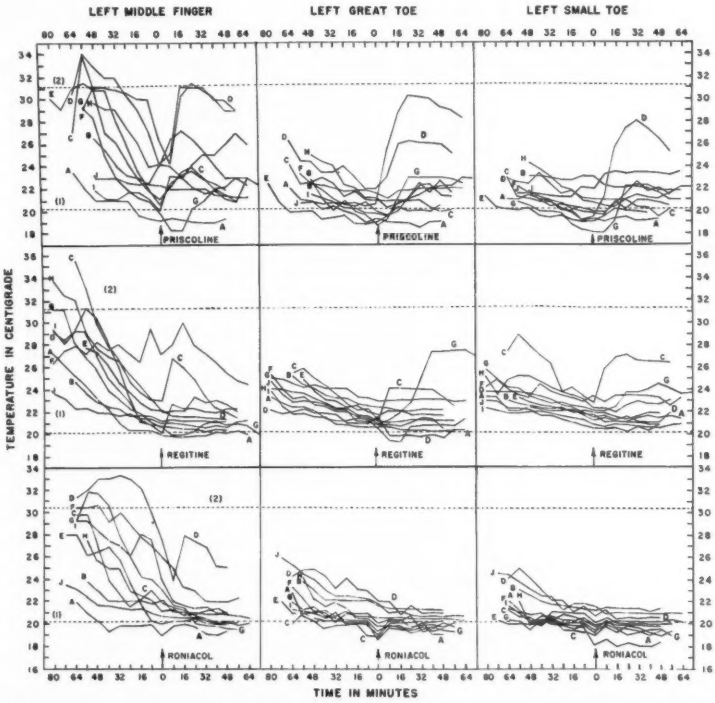


FIG. 1. Graphs of responses to Priscoline, Regitine and Roniacol of 10 normal medical students in whom severe vasospasm was induced by chilling for one or more hours. Top row of graphs: responses to Priscoline (2.0 mg. per kilogram); middle row; responses to Regitine (0.5 mg. per kilogram); bottom row: responses to Roniacol (3.0 mg. per kilogram); first column: responses in left middle finger; second column: responses in left great toe, third column: responses in left small toe; broken line (1) represents average room temperature, broken line (2) represents mean forehead temperature. In each graph the segment to the left of the arrow gives the temperature during the period of chilling required to induce the vasospasm. The segment to the right of the arrow gives the responses to the drug. For additional data see table 1 (A) and table 2.

shown in the average temperatures (table 2, column B).

Systolic arterial pressure fell 14 mm. Hg in one subject and rose 15 mm. Hg on another occasion; diastolic arterial pressure fell 10 mm. Hg on one occasion. In the remainder the pressures remained stable. Side effects noted were chills and shivering during and after the experiment, flushing of the head and neck, and a

those of Priscoline (table 2, column D). The finger temperature increased in six subjects and remained unchanged in four. In four subjects the temperature of the great toe increased, in one subject it decreased, and, one subject demonstrated an initial decrease during the infusion followed by an increase. The left little toe exhibited five increases in temperature and in five subjects the temperature remained essen-

tially unchanged. One subject, GB, demonstrated a moderate response to Regitine, but responded poorly to Priscoline and Roniacol. This drug caused a slightly smaller vasodilation in the hand and about the same vasodilation in the toes as was seen with Priscoline.

Both systolic and diastolic arterial pressure fell on the average 5 mm. Hg. No dramatic increases or decreases were noted. Side effects noted were nasal congestion in all subjects, with but few exceptions flushing of the face, and in a few subjects a metallic taste.

c. *Roniacol.* The range of control temperatures for Roniacol is depicted in the third row of figure 1. The average temperatures are shown in table 2, column E; they are slightly less in the fingers and toes after giving the drug than the control temperatures. In one subject the finger temperature decreased at the commencement of the infusion but rose significantly prior to completion of the infusion; in five subjects no distinct effect of the drug was noted; in four subjects an accelerated drop in finger temperature accompanied the drug infusion. In the left great toe Roniacol caused a very slight increase in one case, an accelerated decrease in temperature in three subjects and essentially no change in six subjects. No significant increase in skin temperature was noted in the left small toe in any subject subsequent to drug infusion. Eight subjects remained stable and three dropped slightly subsequent to the drug injection. A typical finding is that of BG (G) who showed a moderate increase in temperature in response to Priscoline and Regitine but none to Roniacol. AC (A) demonstrated a poor response to all three agents. GB (C) responded well to Regitine but poorly to Priscoline, KB (D) responded well to Priscoline but poorly to Regitine; both responded poorly to Roniacol.

A fall of 20 mm. Hg was noted on one occasion in both systolic and diastolic arterial pressure; on one occasion a decline of 10 mm. Hg systolic pressure was observed, and upon another occasion a 16 mm. Hg fall in diastolic arterial pressure. The arterial pressure, however, generally maintained a steady level in the remaining subjects during the drug injection. Side effects noted were minimal. Several subjects noted a sense of warmth and one noted epigastric pain of a mild nature.

TABLE 2.—*Summary of Average Temperatures of Figures 1 and 2*

	Without Body Warming						With Body Warming								
	Priscoline		Regitine		Roniacol		Priscoline			Regitine			Roniacol		
	Control	Drug	Control	Drug	Control	Drug	Control	Warming	Drug	Control	Warming	Drug	Control	Warming	Drug
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
Left index finger	22.4	25.2	21.9	22.9	23.7	21.9	22.2	31.7	33.0	22.7	32.0	33.4	23.4	29.8	30.7
Left great toe	20.4	23.0	21.3	22.4	20.8	20.5	21.9	22.8	31.5	21.8	23.0	29.1	21.2	22.0	22.7
Left small toe	20.4	22.4	21.0	22.5	20.6	20.0	22.0	23.6	30.4	22.4	22.8	28.7	22.4	23.2	22.8

Control is taken at the point on the graph immediately before the drug infusion in the series with body warming, and the point immediately prior to body warming in the series with body warming. In the Roniacol series the control temperature was taken eight minutes before the drug was given due to the temporary drop in temperature which accompanied the insertion of the infusion needle (see text).

Body warming was taken at the point where the maximal increase in skin temperature occurred.

Drug is the temperature at that point where the maximal response was elicited in cases of increased temperature, and at the end of the infusion period in the case of decrease of skin temperature.

2. *Effects of Drugs with Body Warming.* Figure 2 presents the graphic representation of the temperature changes with body warming plus Priscoline, Regitine or Roniacol. Table 1, part B, gives the range and average room and forehead temperatures and the month each drug was studied on the individuals. Line 1 of figure 2 is the mean room temperature and line 2 is the mean forehead temperature. Table 2 exhibits the average temperatures during the body-warming experiment. Columns H, K, and N disclose the augmenting effect of body

warming prior to drug administration. Body warming promoted a greater increase of blood flow to the fingers than the lower extremities in all three studies. Blood flow to the toes was increased but little by the body warming procedure in all three drug studies. The latter facts substantiate the findings reported in previous papers.[3, 4]

caused excellent vasodilation in both hands and feet.

The arterial blood pressures in this group were stable although a rise in two instances of 15 and 20 mm. Hg was noted. An 18 mm. Hg decrease in diastolic arterial pressure was noted in one instance. Side effects noted in order of their frequency were chilliness, cutis anserina

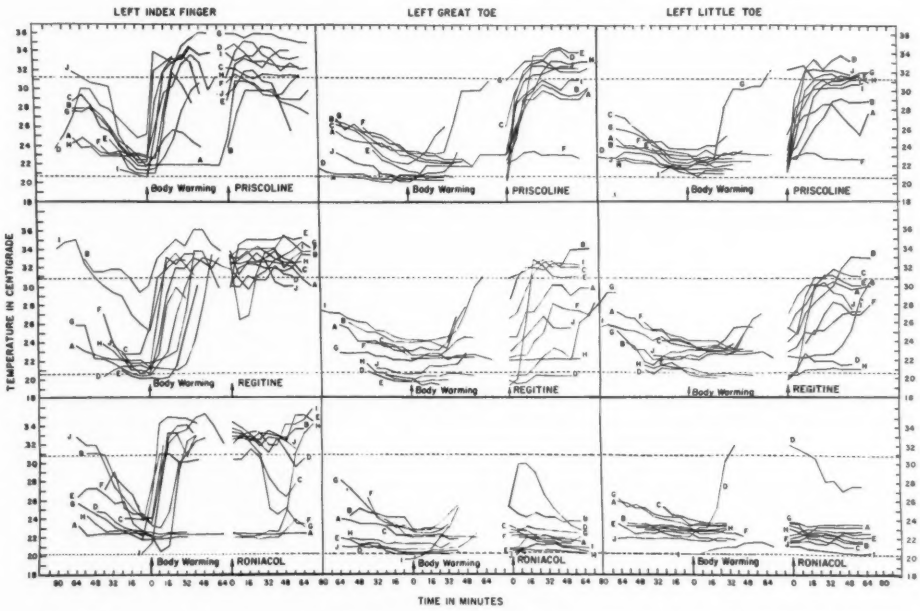


FIG. 2. Graphs of responses to Priscoline, Regitine, and Roniacol of 10 normal medical students in whom a state of moderate vasospasm was induced by chilling followed by body warming. In each graph the segment to the left of the first arrow gives the temperature during the period of chilling. The segments between the first and second arrows gives the temperatures during the period of body warming required to moderate the initial state of vasospasm; the segment to the right of the second arrow gives the temperature during the response to the drug; body warming was continued from the first arrow to the end of the graph. The break in the chart was necessitated by the differences in the lengths of the periods of body warming for the different subjects. The doses were the same as those for figure 1. For other data see figure 1 and tables 1 (B) and 2.

a. *Priscoline.* As shown in figure 2, on five subjects a further increase in temperature of the fingers occurred subsequent to the administration of Priscoline; one exhibited a slight decrease, and the remainder were essentially unchanged. All but one subject AC (F) demonstrated a considerable increase in temperature in both toes following Priscoline. The averages in table 2, column I, demonstrate that the combination of body warming plus Priscoline (goose flesh), flushed face, burning eyes, metallic taste, tingling of the face, slight tachycardia, and heaviness of the eyelids; one subject became nauseated and vomited.

b. *Regitine.* Eight subjects exhibited an increase in finger temperature following drug administration, and two remained unchanged. Regitine produced a moderate increase in the average temperature of the fingers (table 2, column L). All subjects demonstrated an in-

crease in temperature of both toes following drug administration. In two, KG (D) and AS (H) the maximum temperatures reached were not very high. These two subjects had responded well to Priscoline. Subject AC (F), who failed to dilate with Priscoline plus body warming, gave a good response in fingers and toes to body warming plus Regitine. In general the combination of body warming and Regitine resulted in vasodilation in the fingers and toes which was almost as satisfactory as that noted with Priscoline plus body warming (table 2, columns L and I).

Both systolic and diastolic arterial pressures rose on the average of 5 mm. Hg; nasal congestion, scleral injection with smarting, and flushing of the face were noted with the drug.

c. *Roniacol.* The fingers, on the average, exhibited a slight further rise in temperature following Roniacol administration. Three subjects showed no significant change in the temperature of the finger following drug administration; subject AS (H) showed a marked rise after the infusion was discontinued; three other subjects revealed a moderate increase in temperature following administration of Roniacol; one subject exhibited a marked fall during the infusion and one demonstrated a marked fall immediately after the infusion, the remaining two subjects exhibited gradual falls in the skin temperature of the finger following drug administration. A very slight increase in the average skin temperature was noted in the great toe following Roniacol administration (table 2, column O). There was one marked increase in skin temperature of the large toe with a decrease following infusion; four subjects remained stable through the procedure, and five moderate decreases in the temperature of the great toe were noted either during or after the Roniacol administration. A decrease in the average temperature was noted in the small toe following Roniacol administration. In one subject there was a slight increase in skin temperature following Roniacol; four subjects remained essentially unchanged; and in five a moderate decrease in the skin temperature of the small toe was noted. Thus it is seen that Roniacol was capable of improving the vasodilation induced by body warming in the hand, but was unable to induce effective dilation in the feet, even when combined with body warming. In this regard this drug is inferior to Priscoline and Regitine.

Systolic arterial pressure fell 10 mm. Hg in one instance, diastolic fell 10 mm. Hg in another, systolic rose 13 mm. Hg and diastolic 8 mm. Hg in another instance. However, the remainder of the arterial pressures remained stable. Side effects noted were a burning, stinging sensation of the head, face and neck, fairly painful in a few instances, flushing and tingling of the face, metallic taste, burning of the eyes, a slight headache in one case, and mild epigastric pain in another case.

In both studies (with and without body warming) no cases of orthostatic hypotension occurred upon arising, in any of the 60 individual studies.

During the series without body warming the forehead temperatures increased on the average of 1.2 C., range +0.5 to +1.5 C., during the infusion of Priscoline; the skin temperature of the forehead then either remained stable or dropped slightly after terminating the infusion. Regitine demonstrated an average decrease of 0.3 C., range −1.5 to 0 C. Roniacol showed no average change, range +1.5 to −3.0 C. Both of the latter drugs showed either a decrease or stabilization of the forehead temperature subsequent to the infusion.

The body warming procedure, per se, exhibited an average increase of 1.1 C. in the forehead temperature in the Priscoline series, range 0 to +4.0 C. This procedure in the Regitine series showed an average increase of 1.0 C., range −0.5 to +3.0 C., and the Roniacol series showed an average increase in forehead temperature of 0.5 C. with a range of −0.5 to +1.5 C.

In the series with body warming Priscoline exhibited an average increase in forehead temperature during the drug infusion of 1.0 C., range +2.5 to −1.0 C. Regitine showed an average increase in the forehead temperature of 0.1 C., range 0 to +1.0 C. Roniacol showed an average increase in forehead temperature of 1.0 C., range +2.5 to −1.0 C. In all three

drugs in this series the forehead temperature either stabilized or decreased slightly subsequent to termination of infusion.

Discussion

It is of interest to note that the tabulated results of Priscoline in this paper demonstrate that the maximum cutaneous temperatures reached were not as great in this work as in a previous study.[3] The room temperatures, in the previous studies fluctuated more than in the present study; and the air velocity in this study was 60 ft. per minute as compared with 25 to 50 ft. per minute in the previous experiments.[3] These factors might well account for the differences in cutaneous temperatures noted after Priscoline in the two studies.

Priscoline and Regitine compared favorably in the series without body warming. Priscoline demonstrated a slightly better efficiency in increasing the blood flow in the finger. Priscoline also increased the temperature in the fingers and toes in a slightly larger number of subjects than did Regitine. Roniacol, in the doses used, demonstrated little ability to cause vasodilation in the absence of body warming, the increased blood flow being very meager. Roniacol in only one instance exhibited an increase in blood flow of the upper extremity, and showed no adequate increases in blood flow of the lower extremities.

It was noted that the body warming procedure, per se, was the most valuable method to promote increased blood flow in the upper extremities. In many cases maximal temperature was induced in the fingers by body warming per se; in others maximal temperature was obtained only by the combination of body warming plus a drug. Regitine plus body warming induced the highest temperatures in the finger. Priscoline plus body warming caused on the average the highest maximal temperatures in the toe; Regitine, with body warming, duplicated the beneficial results of Priscoline, but to a slightly lesser extent.

Roniacol again offered little increase in blood flow when administered with body warming. Only one subject manifested a result worthy of note. Three of the subjects demonstrated a decrease of the finger temperature subsequent to infusion, as did four in the great toe and five in the small toe. This drug in the dose used is apparently not a very effective vasodilator.

It is interesting to note that, in the series without body warming, particularly in the Roniacol series, and also occasionally in the series with body warming, a sudden decrease in skin temperature occurred immediately upon insertion of the infusion needle with usually a return to the preceding temperature 8/16 minutes after the beginning of the infusion. This change occurred in some instances in both the upper and lower extremities of the same individual in the same drug run, in other instances it occurred only in one of the extremities. The etiology of this sudden but moderate temporary decrease in skin temperature is unknown.

It is quite apparent that Priscoline and Regitine are more effective in this study in overcoming vasospasm. Priscoline offers perhaps a slightly better dilating effect than Regitine. Regitine, however, with its less unpleasant side effects is to be considered seriously. Both drugs exhibit the ability to cause increased blood flow to the extremities, and should be tested clinically for their relative efficacy of performance in peripheral vascular diseases.

While this study demonstrates the ability of Priscoline and Regitine to overcome vasospasm, the exact mechanism of action is unknown. Whether they act by blocking epinephrine or the action of sympathin at the nerve endings is unknown. However, since the effects are similar to those of spinal anesthesia, the drugs probably act at least in part by blocking sympathetic nerve impulses.

Summary

1. Vasoconstriction induced by a low temperature room and vasodilation induced by drugs and by body warming have been measured on 14 normal subjects in this study. The measuring instruments were potentiometers and thermocouples.

2. The method was used to test the efficacy of the drugs in overcoming vasospasm in the normal subjects in order to evaluate the pos-

sibility of their subsequent usage in peripheral vascular diseases.

3. Severe cutaneous vasospasm was induced by exposure of the lightly clad subject to an environmental temperature of 20 C. for one hour or more. In half the tests the severe vasospasm was reduced to moderate vasospasm by application of heat to the torso of the chilled subjects.

4. Sixty individual studies were performed, 20 on each of three drugs. These drugs were Priscoline, Regitine, and Roniacol. Ten studies were performed on each drug without body warming, and 10 with body warming. Body warming was induced with two heating pads applied to the torso and covered with a blanket.

5. The drugs were administered intravenously over a period of approximately one half hour in the dosage of Priscoline 2.0 mg. per kilogram, Regitine 0.5 mg. per kilogram, or Roniacol 3.0 mg. per kilogram dissolved in 200 ml. of 0.9 per cent saline.

6. It was discovered that Priscoline and Regitine are both fairly good vasodilators especially in the upper extremities. In the series without body warming, Priscoline proved to be slightly better. Roniacol gave poor results. No dangerous or painful untoward reactions were noted with any of the agents.

7. In the body warming series it was noted that body warming, per se, gave better vasodilation in the upper extremity than any of the drugs tested. All three drugs aided slightly blood flow to the upper extremities, subsequent to body warming; the order of efficacy was Regitine, Priscoline and Roniacol.

8. Body warming, per se, proved of little use in increasing the blood flow to the lower extremities. Priscoline during body warming augmented the lower extremity flow greatly. Regitine did quite adequately also. Roniacol exhibited no significant results. No untoward side effects were observed.

9. Forehead temperatures were increased by Priscoline alone, by body warming alone, and further increased by Priscoline and Roniacol when given during body warming.

10. Comparative clinical trial of Priscoline and Regitine plus body warming is advised to further substantiate their efficacy as vasodilators in vasospastic peripheral vascular diseases involving the upper or lower extremity. Roniacol plus body warming may be effective in the treatment of vascular spasm involving only the upper extremity.

ACKNOWLEDGMENT

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Aconitine-Induced Auricular Arrhythmias and Their Relation to Circus-Movement Flutter

By BARBARA B. BROWN, PH.D. AND GEORGE H. ACHESON, M.D.

Certain characteristics of aconitine-induced auricular arrhythmias in dogs and the responses of aconitine-induced flutter to various experimental procedures and to drugs are described. In certain experiments there was evidence that a secondary flutter mechanism had developed which, in some instances, resembled flutter of circus-movement origin. When aconitine-induced and circus-movement flutters were induced separately and simultaneously in auricles functionally divided by a crush, they responded to drugs in their characteristic manners. Aconitine-induced flutter slowed progressively and recovered gradually to flutter, whereas circus-movement flutter frequently reverted suddenly and permanently to sinus rhythm.

SCHERF and co-workers have reported certain of the phenomena occurring upon the local application of aconitine to the dog's auricle.[1–4] These authors gave evidence that the arrhythmias arising from this procedure are maintained by the artificial source of impulse production and not because a circus movement arises. On the other hand, experimental auricular flutter of circus-movement origin has been well-defined by Rosenblueth and García Ramos.[5] In spite of the distinct characteristics of these two types of experimental auricular flutter, the existence of the latter is denied.[6–8] The present work was undertaken primarily to determine the effects of certain substances on both the aconitine-induced and circus-movement auricular flutters. During the investigation it was found that auricular arrhythmias of two different sources might exist either simultaneously or subsequently in the same auricle, and further, that two flutters of different origins could be induced simultaneously in the same auricle. This report thus deals mainly with the distinctions which can be made between experimental auricular flutters of different origins.

METHOD

The experiments were conducted in dogs, weighing between 15 and 23 Kg., anesthetized by the intraperitoneal injection of 0.7 cc. per kilogram of Dial with urethane solution (Ciba). Blood pressure was recorded from the carotid artery. Auricular electrograms were recorded, and the ventricular complex was taken from pericardial tissue near the ventricular apex. Injections of compounds under study were made into the external jugular vein. The reported results were obtained in dogs in which the blood pressure was at least 60 mm. Hg and rectal temperature was maintained at 37 C. by external heat.

Two methods for inducing auricular flutter were employed. The first was induced according to the method of Scherf[1] in which 0.05 cc. of a 0.05 per cent solution of aconitine nitrate is injected subepicardially near the tip of the right auricle. Circus-movement flutter was induced according to the method of Rosenblueth and García Ramos[9] in which flutter is initiated by brief, rapid electrical stimulation near a crushed area on the right auricle. The precise method used in the present study has been fully described.[10, 11]

Changes in electrical activity in the auricle were recorded from pairs of silver electrodes with small interelectrodal distance (2 to 3 mm.) which were clipped lightly to the auricular muscle. All recordings were made by means of a four channel ink-writing oscillograph (Grass, model IIA), and were made continuously during all experiments. Differences in rate and wave form between impulses recorded near the aconitine site and those recorded at a distance during aconitine-induced flutter were noted in a number of experiments. In most experiments (except those described in part B, below), the differences were minor and disappeared upon changing the orientation of the distant electrodes. In some instances the relation between position of recording leads and direction of the impulse accounted for apparent irregularity, alternation or even regularly occurring missed beats, since these could be eliminated by changing position of the electrodes.

The effect of stimulation of the cardiac nerves was

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determined during both types of flutter. Maximal nerve stimulation (using a Grass 3C stimulator, square waves) was effected by using the lowest frequency of stimulation which slowed or accelerated the ventricle significantly and a voltage above which no further change could be produced. For the cut central end of the vagus this was stimuli of 0.2 or 0.5 millisecond duration at a frequency of 10 to 30 per second and a voltage of 10 to 20. The sympathetic chain was stimulated by placing the electrodes between the stellate and ganglion of T-2, after freeing the chains of all connections except the postganglionic fibers arising from the stellate ganglion, using a pulse duration of 0.01 millisecond, a frequency of 2 or 60 per second, and a voltage of between 20 and 40.

Observations

A. *Characteristics of Aconitine-Induced Auricular Arrhythmias*

The auricular changes brought about by the local application of aconitine were studied in 39 dogs. The innervation was intact in most instances. The auricular rate began to increase within 10 to 100 seconds (average of 26 ± 2.2 seconds) after injection of the aconitine in 33 of the experiments, and the total time interval until an auricular rate of 300 beats per minute or more was reached averaged 41 ± 4.2 seconds. In three experiments a rapid arrhythmia occurred immediately after injection of the aconitine, while in three other experiments no increase in auricular rate occurred for several minutes and a rate of 300 or more was not reached for nearly five minutes. The time necessary to reach a steady rate (variation less than 20 beats per minute) averaged 222 ± 21 seconds for all 39 dogs.

The character of onset of the aconitine arrhythmia was different in different dogs and bore no relation to whether a regular flutter or a fibrillation developed. In 17 experiments the most marked increase in auricular rate occurred within one cycle of the previous sinus rate. In 14 of these experiments, the sudden increase appeared 27 ± 4.3 seconds after injection of the aconitine and averaged 148 ± 12.8 beats per minute; in one experiment the sudden increase amounted to 430 beats per minute, in another experiment to 30 beats per minute, whereas in a third dog the rate jumped rapidly and suddenly several times and was not counted. In the remaining 22 experiments, the onset was less sudden, and the arrhythmias developed to their maximal rate over a period of 30 to 90 seconds. Full development of these 22 arrhythmias occurred sometimes as a regular steady increase, sometimes irregularly (ectopic beats, coupling, and runs of fast beating), and sometimes as alternating fast and slow rhythms. The steady rate attained in most experiments was less than the rate developed within the first several minutes.

The criteria for flutter, as the term is used in this paper, are continuing regularity of rapid beating with regular wave form and a variation from the average rate developed of less than 20 beats per minute over a period of 10 to 30 minutes. Regular flutter occurred in 29 of the 39 dogs, and had an average rate of 430 ± 16 beats per minute. The lowest steady flutter rate recorded was 300 beats per minute and the highest was 600 beats per minute.

Auricular fibrillation, defined in terms of high rate and erratic wave form, occurred in 10 of the dogs. Auricular rates in these experiments ranged between 660 and 1080 near the aconitine site. In four experiments a fourth or more of the impulses recorded near the aconitine site could not be obtained at distant electrodes. In eight experiments the fibrillation was persistent; in two it changed to a flutter after a few minutes. The instances of persistent fibrillation could be converted into flutter by the injection of one or another of the substances under study.

Duration of the arrhythmia induced by the standard injection of aconitine was not studied specifically. The regular auricular flutter which occurred in the 29 dogs usually persisted longer than two hours in spite of intermittent slowing produced by the injection of drugs.

The results reported below were obtained in well-stabilized flutter.

Effect of Experimental Procedures. Aconitine-induced flutter responded to changes in the innervation (fig. 1) in the same direction as circus-movement flutter.[10] Section of one vagus nerve increased slightly both the flutter and the ventricular rate, and section of the other vagus caused an additional increase. Complete vagotomy occasionally had no effect, while in

some experiments both auricular and ventricular rates were increased by amounts up to 20 per cent. Stimulation of the vagus caused a marked increase when the flutter rate was high (250 or more) but only about a 5 per cent increase when the flutter rate was low. Irregular arrhythmias frequently changed to regular flutter during vagal stimulation. This change to a regular beating was noted by Lewis and coworkers who attributed the change to a shortening of refractory period.[12, 13] Stimulation of the sympathetic chain also caused an increased flutter rate of approximately 5 per cent.

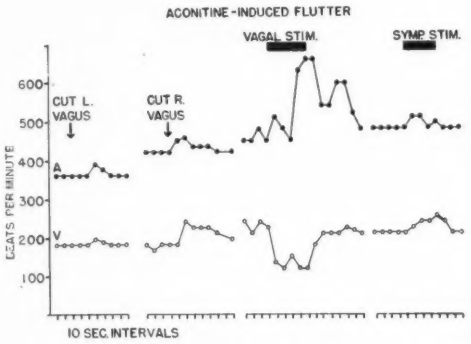

FIG. 1. Effects of changes in the innervation of the heart on aconitine-induced auricular flutter. In this and other figures A and V indicate auricular and ventricular rates.

In confirmation of Scherf,[1] cooling the site of aconitine injection often decreased the auricular rate (fig. 2). The degree of slowing was dependent upon the intensity of the cold. Stretching the auricle often increased the rate of flutter. Further, it was usually found that, as noted by Scherf,[1] the arrhythmia disappeared upon isolation of the aconitine-containing portion of the auricle by clamping and reappeared upon removal of the clamp (fig. 4.1). Often a period of one to two minutes was required before the clamping procedure completely blocked the influence of impulses from the aconitine site on the rest of the auricle. At the same time the rate in the isolated tip often decreased. These changes suggest that interference with circulation plays a part in impulse propagation under these circumstances.

Effect of Drugs. The effects of procaine and the related substances, diethylaminoethanol (DEAE) and β-diethylaminoethyl 2,4-dichlorobenzoate (DCB) and also of quinidine were evaluated in aconitine-induced flutter. Their effects in auricular flutter of circus-movement origin have been reported previously.[10, 11]

A similar course of events followed the intravenous injection of any one of these compounds and is illustrated in figure 2. The auricular rate began to slow within a minute, and maximal slowing occurred in two to five minutes. The degree and duration of slowing increased as the dose was increased. Doses of 4 mg. per kilogram of all substances except DEAE generally caused slowing to or near to the sinus rate. Doses of 32 mg. per kilogram of DEAE produced similar effects.

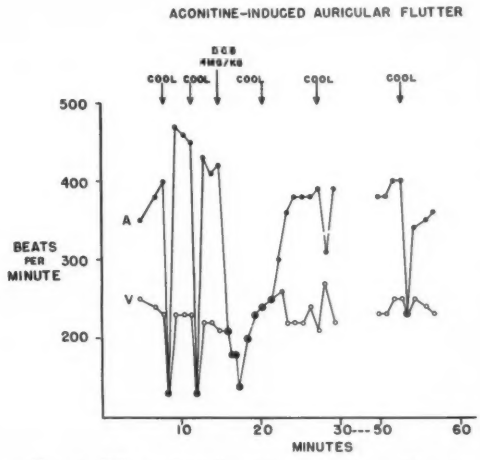

FIG. 2. Effect of cooling the area of aconitine injection, and effect of injection of β-diethylaminoethyl-2,4-dichlorobenzoate (DCB) on aconitine-induced flutter in heart with intact innervation.

In about 50 per cent of the experiments the sinus node became the pacemaker when the rate of impulse formation at the aconitine site was depressed below that of the sinus node. This change of pacemaker was indicated in the electrograms as a reversal of the path of the conduction wave (fig. 3). The positions of the recording electrodes were in a line between the site of aconitine injection and the region of the sinus node. When acute drug effects had worn off, the path of the wave again reversed in di-

rection. Ectopic beats became more frequent until the aconitine site regained control of beating. Recovery to approximately the original flutter rate usually occurred within 15 to 25 minutes. The recovery was gradual and was either regular or irregular regardless of whether or not a change to sinus rhythm had occurred. These phenomena are in sharp contrast to the sudden and permanent reversion from a high rate of flutter which occurs in circus-movement flutter.[10]

During recovery from maximal slowing, the response of the aconitine site to application of cold could not be elicited; it remained somewhat depressed after recovery to original flutter rate (fig. 2).

induced flutter to drugs differs from that of circus-movement flutter in that sudden (within one beat) and permanent reversions do not occur. In certain experiments, however, atypical responses to these procedures were obtained.

Unusual behavior of the aconitine-induced flutter appeared in 10 of the 29 dogs in which a regular flutter was elicited. In 5 of the 10 animals, the rapid injection of DCB or procaine resulted in a sudden (within one beat) reversion to sinus rate from a high rate of flutter (350 to 560 beats per minute)—a characteristic of experimental circus-movement flutter. Although in these five animals the reversions were permanent, occasional ectopic beats sometimes occurred for a short period after reversion, suggesting that activity at the aconitine site occasionally became effective in producing a response. Further, in two of these experiments in which reversions were subsequently observed, functional separation of the aconitine-containing site from the rest of the auricle, by clamping with rubber-sheathed hemostats, did not result in a disappearance of the flutter in the body of the auricle. Coordinated activity in the isolated aconitine-containing portion fell to zero although considerable minute disorganized activity was recorded, while a regular flutter remained in the rest of the auricle (fig. 4*B*). The clamping procedures were carried out soon enough after injection of the aconitine to ensure minimal diffusion into surrounding auricular tissue, and while the injection wheal was still visible. Rapid injection of one of the compounds

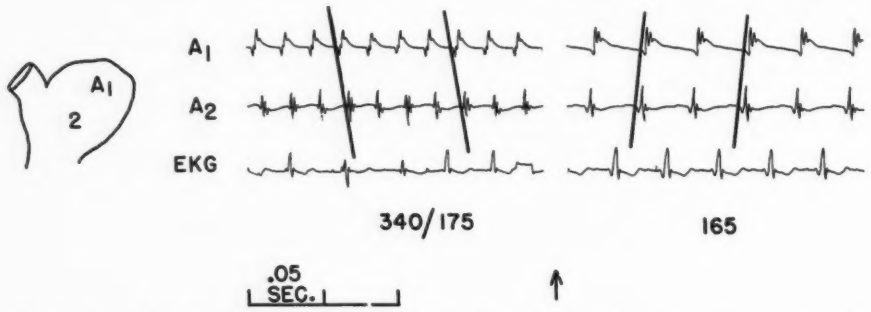

FIG. 3. Auricular electrograms (A_1 and A_2) illustrating change in direction of conduction of the auricular wave from aconitine site to sinus node following marked slowing of aconitine-induced flutter caused by injection of a drug (at arrow).

The ventricular rate in innervated hearts was decreased by diethylaminoethanol (DEAE) and its dichlorobenzoic acid ester (DCB), but it was frequently increased by procaine and by quinidine in doses which did not cause a rapid decrease in auricular rate.

B. *Indications that a Secondary Mechanism May Arise Spontaneously*

The responses of aconitine-induced flutter to cooling, stretching, clamping and vagal stimulation were employed by Scherf[1, 2, 3] as evidence that a single focus of rapid impulse formation and not circus-movement was the mechanism responsible for this arrhythmia. As noted in the previous section, confirmatory results were obtained in many experiments. Further, it was demonstrated that the response of aconitine-

during a clamping period in one experiment resulted in a prompt and permanent reversion to sinus rate.

The five experiments cited above show that in some instances of aconitine-induced flutter (a) reversions characteristic of circus-movement flutter occur, and (b) isolation of the aconitine-containing auricular tip does not affect flutter in the body of the auricle but eliminates it from the tip. These observations indicate that a flutter mechanism secondary to the original aconitine had developed and was responsible for

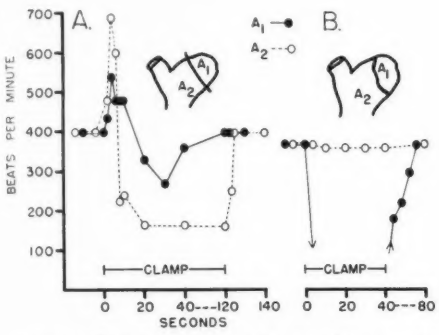

FIG. 4. Effect of isolation of the aconitine-containing auricular tip (A_1) from the rest of the auricle by clamping. In *A* the tip continued to flutter whereas the remaining auricle reverted to sinus rhythm for the duration of the clamping period. In *B* no coordinated activity was recorded at the tip during clamping whereas the flutter continued in the rest of the auricle.

maintenance of the arrhythmia. The secondary mechanism could be either a second ectopic focus or circus-movement flutter. The sudden and permanent reversions which occurred imply an impulse circuit. In these five experiments the aconitine was no longer the predominant factor maintaining the arrhythmia; it was depressed in its activity to such an extent that it was completely displaced by a secondary flutter mechanism.

A somewhat different situation was found to exist in the other five experiments in which unusual behavior of the aconitine-induced flutter was noted. In three of the experiments, cooling the site of the aconitine injection resulted in an increased rate (rather than a decrease) and stretching the auricle resulted in a decreased rate of flutter (rather than an increase) (fig. 5). The responses were not confined to the aconitine area but were recorded at distant areas as well. These phenomena could result from an unusual response of the auricular tissue at the aconitine site in these animals. The phenomena

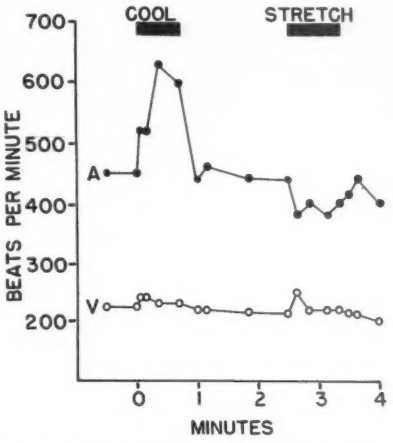

FIG. 5. Unusual responses to cooling the site of aconitine injection and to stretching the auricle during aconitine-induced auricular flutter.

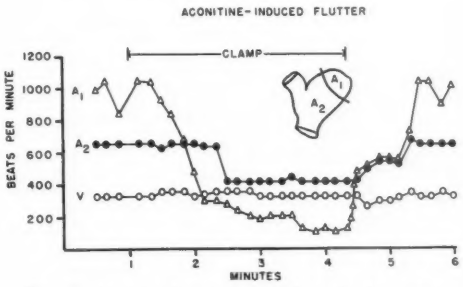

FIG. 6. An experiment in which auricular rate was different in different areas, and separation of the aconitine-containing auricular tip from the rest of the auricle resulted in further differences. For description, see text.

could also be explained by assuming interaction between impulses spreading from the aconitine site and those from a secondary mechanism, permitted by changes in refractoriness.

More striking evidence that a secondary mechanism may be simultaneously active was encountered in the other two experiments and a third obtained more recently. Auricular elec-

trograms in these experiments showed that the aconitine-induced flutter did not have the same rate in different parts of the auricle. In the experiment graphed in figure 6, a very high (1000) and fairly regular beating was recorded near the site of the aconitine injection (A_1). The second lead, about 3 cm. further away, recorded a slower (660) and regular beat (A_2). This difference could mean that many of the beats from A_1 did not reach A_2. In order to test this, A_1 was isolated from A_2 by clamping. As a result, activity at A_1 fell within one minute to about 300 beats per minute and to 120 in the following two minutes. The auricular rate at A_2 remained at 640 to 660 for one and one-half minutes, then suddenly fell, but was still fluttering at 420 beats per minute. When the clamp was removed, activity at A_1 returned in about one minute to its original high level. A_2 followed this return until it also reached its original level. The maintenance of flutter rates at A_2 during clamping indicates the independent existence of a secondary mechanism. The abrupt change in its rate may be attributed to either (a) a fortuitous change in the mechanism of the secondary arrhythmia, or (b) exclusion of impulses from the aconitine source which had until then interfered with the activity of the secondary mechanisms. The complete regularity of rates at A_2 and the abruptness of its change during clamping suggest that the secondary mechanism may have been circus-movement in origin. If the secondary mechanism were an ectopic focus, withdrawal of the aconitine interference might permit an increase of rate by removing refractory barriers. If, on the other hand, the secondary mechanism were circus-movement, removal of refractory barriers would permit a longer circus, and hence a slower rate. The second group of experiments thus indicated that the secondary mechanism can exist independently and simultaneously with the aconitine flutter.

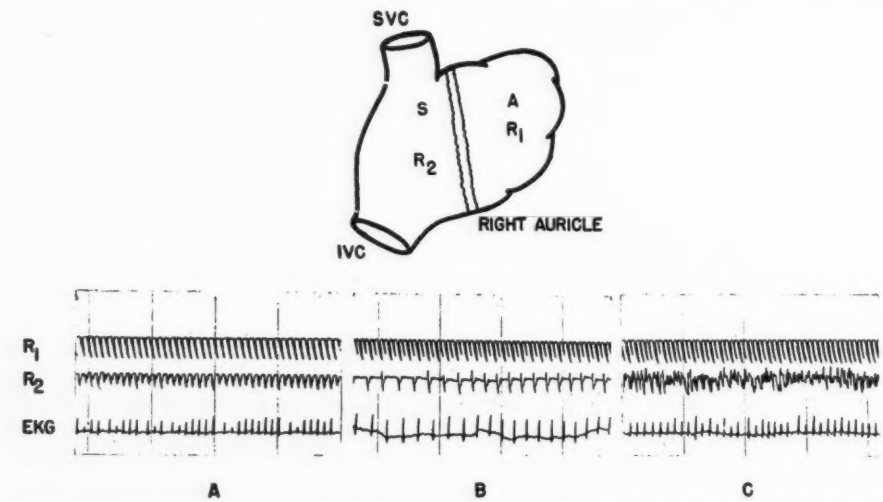

FIG. 7. Development of two arrhythmias in the same auricle. Record *A* was obtained after injection of aconitine at point A (in diagram) and before dividing the auricle by an encircling crush. Record *B* was taken after crushing and shows the aconitine flutter recorded at R_1 and the return to sinus rate at R_2. Record *C* was taken after brief stimulation at *S* had resulted in an arrhythmia in the atrial portion removed from the aconitine.

C. *Circus-movement Flutter and Aconitine Flutter Induced Separately and Simultaneously in the Same Auricle*

These experiments were conducted as indicated in the diagram of figure 7. R_1 and R_2 are pairs of recording electrodes; S is a pair of stimulating electrodes. Aconitine was injected at site A, and the resulting flutter, recorded at both R_1 and R_2, is shown in the first record (A). A few minutes later the auricle was di-

vided by an encircling crush made by a large hemostat. Complete isolation of the auricular from the atrial portion was indicated in the electrograms taken from R_2 which changed from flutter to a sinus rate (record B, figure 7). Electrical stimulation was then applied at point S to induce a circus-movement arrhythmia in the remaining auricle, atrium or around the great veins. Record C shows the arrhythmia which was initiated by stimulation. It was irregular and rapid, with a rate of 540 beats per minute. At the same time, the aconitine-induced flutter was regular and had a rate of 400 beats per minute.

In these experiments, the rate of the aconitine-induced arrhythmia averaged 410 ± 26 beats per minute in 11 hearts, and the rate of the circus-movement flutter averaged 455 ± 32 in 10 experiments. In one heart the rate of the circus-movement arrhythmia was 1080 beats per minute. Eight of the hearts studied had intact innervation, and three hearts were studied also after decentralization by section of the vagi and upper thoracic sympathetic roots. Brown and Acheson[10] found circus-movement flutter to have an average rate of 472 ± 8.2 in 36 hearts with intact innervation.

The simultaneously existing flutters responded to cooling of the aconitine site or the ventral and lateral walls of the atrium in the same way as when they existed separately in an auricle; the aconitine flutter decelerated while the circus-movement flutter was unaffected. The responses to nerve section and stimulation, however, were variable probably because of damage to nerve pathways by the encircling crush. In general, section of one vagus nerve or stimulation of the sympathetic chain caused no change in rate. For a brief period after section of both vagi episodes of fibrillation of the aconitine-induced flutter occurred, but the circus-movement flutter did not change in rate. Vagal stimulation usually caused an increased rate of the aconitine flutter, but either increased, decreased, or did not change the rate of the circus-movement flutter.

Effects of the drugs described in part A were similar to those obtained when each flutter ex-

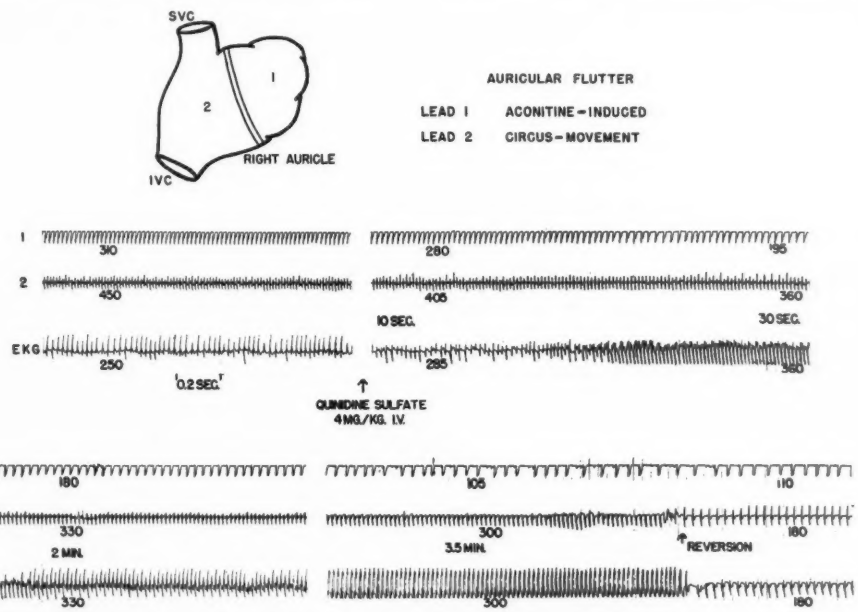

FIG. 8. The effect of quinidine on aconitine-induced and circus-movement flutters in the same auricle in a heart with intact innervation. Marked slowing to below the sinus rate occurs in the aconitine flutter; the circus-movement flutter slows and then reverts to sinus rhythm; the ventricle at first increases in rate, then follows the circus-movement flutter.

isted singly in an auricle. A typical record is shown in figure 8. In this experiment the effects of quinidine on both the circus-movement flutter and on the ventricular rate in the innervated heart are the same as those previously described.[11] The atrial flutter slowed markedly and suddenly reverted to sinus rate three and one-half minutes after the injection of quinidine. The aconitine-containing portion slowed rapidly and fairly regularly until the rate was below that of the sinus rate. The auricular tip cannot be governed by the sinus node because it is isolated from it. Activity in the aconitine-containing portion eventually returned to the original flutter rate even in experiments where activity had been temporarily reduced to zero by drug injection, whereas the atrial portion remained at sinus rate until subsequent stimulation was employed to reinduce flutter.

Discussion

In the present series of experiments, the arrhythmias induced by local application of aconitine were of higher rate and longer duration, and showed a higher incidence of fibrillation than those of a comparable series reported by Scherf using the same injection site near the auricular tip.[1] The discrepancies may be ascribed to the fact that Scherf used a lead II electrocardiogram, whereas in the present experiments two or more direct auricular leads were employed. It has been noted under Method that certain apparent conduction failures were artefacts due to the relation between position of recording leads and the path of the impulses. Further, not all waves from a rapidly firing focus may be conducted as far as distant electrodes. At rapid auricular rates it is unlikely that all the waves produced at the aconitine site are evident in lead II.

The drugs studied slow the rate of flutter induced by aconitine. They also increase the effective refractory period of the auricular wall, but to a degree which still permits the auricle to conduct at a relatively rapid rate of beating.[11, 14] When the aconitine-induced flutter is markedly slowed, the sinus node becomes the pacemaker because its rate of beating is more rapid. From these facts it seems unlikely that effective refractory period is the principal factor responsible for the slowing of the rate of flutter. The drugs, therefore, may be presumed to decrease the rate of impulse formation at the aconitine site. In addition, in the presence of rapid responses of auricular tissue, acetylcholine can increase impulse production.[15] The acceleration of acocitine-induced flutter by vagal stimulation may depend upon this effect. It should be noted that the aconitine site is much more sensitive to all of these effects than is the sinus node.[14]

In aconitine-induced flutter, changes of conduction velocity would not influence the number of impulses recorded from a given site at a distance from the focus of impulse formation. In contrast, slowing or acceleration of the rate of circus-movement flutter depends upon slowing or acceleration of the conduction velocity of the impulse. During aconitine-induced flutter, an ectopic focus is present as long as the aconitine effect lasts; recovery of rate of flutter following the depression of impulse formation produced by drugs represents simply the disappearance of the drug effect. In contrast, reversion occurs in experimental circus-movement flutter when the circus wave is abolished; there is no ectopic focus. A drug designed to revert circus-movement flutter need act only long enough to produce the appropriate changes of conduction velocity and effective refractory period.

Scherf and co-workers[16] have reported that the auricular fibrillation induced by electrical stimulation or by the local application of acetylcholine at the sinus node did not slow on cooling this area, but usually slowed when both the sinus and A-V areas were cooled simultaneously. They suggested that in these instances the fibrillation was due to multiple foci of rapid impulse formation, one or more of these foci being in the area of the A-V node. They noted that multiple foci rarely occurred following induction of fibrillation with aconitine. In contrast to this, the experiments described in part B provide evidence that a secondary mechanism *can* develop in aconitine flutter and may contribute to or be responsible for maintenance of the arrhythmia. When the nature of the flutter is unknown, as in these instances, it may be deduced from its responses to procedures which have characteristic effects in either aconitine-induced or circus-movement flutter. The

procedures carried out in these experiments in some instances did not exclude the possibility of a second ectopic focus. In other instances, in which the influence of the aconitine focus was eliminated, the complete regularity of rates of the secondary flutter (fig. 4, 6), the abruptness of changes of rate (fig. 6), and the occurrence of permanent reversion, suggested that the secondary mechanism was a circus. On the other hand, it is conceivable that impulse production from certain kinds of ectopic focus, once established, may be self-sustaining only above a critical rate of firing, and that the action of a drug which slows the firing below this rate therefore abolishes the focus.

Summary

1. The characteristics of aconitine-induced arrhythmias were studied in 39 dogs. Auricular fibrillation occurred in 10 hearts; flutter occurred in 29 hearts. When the auricular flutter was regular and persistent, responses to cooling and stretching the auricle, and to nerve section and stimulation were determined. Most of the results can be accounted for by the changes in impulse production of the aconitine site.

2. Unusual behavior of the aconitine-induced flutter appeared in 10 of the 29 hearts in which flutter was regular and persistent. It was demonstrated by various procedures that a secondary mechanism had developed and that the aconitine-induced ectopic focus was either displaced by the secondary mechanism or existed simultaneously with it.

3. Circus-movement and aconitine-induced flutters were induced separately and simultaneously in auricles functionally divided by a crush. The two flutters responded differently and characteristically to the injection of drugs.

4. Both circus-movement and aconitine-induced flutters are decelerated by certain drugs. Circus-movement flutter may revert suddenly and permanently from a high rate to sinus rhythm: aconitine-induced flutter slows progressively to a sinus rate and recovers gradually to the original level.

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The Clinical Significance of Postextrasystolic T-Wave Changes

By Harold D. Levine, M.D., Bernard Lown, M.D., and Richard B. Streeper, M.D.

Examination of the T wave of the beat following the pause occurring in many conditions, notably premature systoles, may show variations from the regular T waves in the same lead without concomitant change in the QRS complex. This phenomenon, when pronounced, is generally associated with evidence of myocardial impairment and is correlated with abnormal reaction to stress tests for coronary insufficiency. Inquiry is here made into the factors affecting this phenomenon, its mechanism, topography, persistency and clinical significance.

THE QRS complex and the T wave do not ordinarily vary in form after an extrasystole. Occasionally, however, one notices that the T wave immediately after a compensatory pause undergoes alteration either in size, shape or direction without modification of the antecedent QRS complex. This change is exemplified in figure 1 recorded in a man 58 years old with an old anteroseptal infarction. In lead V_3 particularly, the T waves, from being upright in the regular complexes, have become diphasic in the beat after the compensatory pause, with a pronounced terminal inversion. In terms of Wilson's formulation such changes must be regarded as "primary" since they are not predicated upon alterations in the QRS complex. They are indicative of a change in the electrical recovery or repolarization of the heart.

Though this phenomenon has received some attention in the experimental and clinical literature to date, no systematic study is available which sets forth criteria for evaluating the significance of such changes, establishes its incidence or assesses its clinical import. The object of the present report is threefold: first, to determine whether a disturbance in repolarization which is limited to the postextrasystolic beat is associated with clinical evidence of myocardial damage; second, to observe whether the absence of T-wave changes in the beat immediately following the compensatory pause reflects the lack of demonstrable heart disease; and third, to correlate the presence or absence of such T-wave changes with the result of the Master two-step test for coronary insufficiency.

From the Medical Clinic of the Peter Bent Brigham Hospital and the Department of Medicine, Harvard Medical School, Boston, and the Heart Disease Epidemiology Study, National Heart Institute.

Methods and Material

The T wave of the beat following a compensatory pause (that is, the postextrasystolic T wave) was compared with the T wave of the regular ventricular complexes in the same lead and characterized as either "positive" or "negative." A T-wave change to be considered "positive" had to fulfill at least one of the following criteria: (1) a definite total change in the direction of the T wave; (2) a change to a diphasic form with the major portion having a direction opposite that of the original T wave; (3) a change in T wave voltage of 2 mm. or more; or (4) a change in amplitude of less than 2 mm. when associated with a prolongation of the Q-T interval by 0.05 second or more. These arbitrary criteria define an alteration which is striking and clearly present at first sight. Before judgment was passed on a postextraxystolic T-wave change, premature beats had to be frequent and present in extremity and precordial leads. These criteria of positivity had to be fulfilled without alteration of the immediately preceding QRS complex. The "secondary" T-wave changes not uncommonly seen after interpolated ventricular premature beats were not characterized as "positive." Patients with persistent bigeminal rhythm were excluded from consideration since in this disturbance of rhythm every other T wave is postextrasystolic, the alternate T waves belong to the premature beats, and no normal T waves exist as a basis for comparison. All individuals in this survey had multiple leads including three conventional and three unipolar limb leads and six unipolar chest leads.

Three principal categories of patients were studied: a group of 62 patients exhibiting positive postextrasystolic T-wave changes; a group of 77

individuals with negative postextrasystolic T-wave changes; and 26 individuals with frequent premature beats upon whom a Master two-step test was performed. In each instance the electrocardiogram was studied and a judgment whether the T-wave change was positive or negative was made prior to a perusal of the case history or the result of the Master test.

The population constituting the positive postextrasystolic T-wave group consisted of 30 observed in the routine reading of electrocardiograms at the Peter Bent Brigham Hospital. Twenty patients exhibiting this change were found in a concurrent study of the relation of auriculoventricular conduction time to paroxysmal rapid action of the heart[1] and the remaining 12 were discovered in a group of 50 individuals with frequent premature beats examined in the cardiovascular survey of the population of Framingham, Massachusetts, now being conducted by the National Heart Institute of the United States Public Health Service.

The group with negative postextrasystolic T-wave changes serving as a control population was derived in a similar fashion. Thirty-nine were found in the routine reading of cardiograms and 38 were detected in the above-mentioned mass population survey for heart disease. As a further check on the clinical significance of absence of T-wave changes in the postextrasystolic beat an additional group was studied. Instead of using the electrocardiogram as the starting point in selection, patients were chosen on the basis of the diagnosis of functional heart disease. From a group of private patients diagnosed by Dr. S. A. Levine as having functional heart disease 62 were selected because they had frequent premature beats.

The 26 patients who had the two-step stress test had a so-called "single" Master test with the standard number of climbs defined for their respective sex, weight and age. This group was selected on the basis of frequent extrasystoles from among 300 individuals who had such a stress test.

Results

A. Incidence and Significance of Positive Postextrasystolic T-Wave Changes.

Of 2143 consecutive electrocardiograms taken at the Peter Bent Brigham Hospital 161 tracings showed premature beats. Twenty-two of these exhibited positive postextrasystolic T-wave changes. This indicates a rough incidence of one positive change in 100 routine electrocardiograms, or one in seven tracings showing premature beats.

The etiologic background of 62 patients with positive postextrasystolic T-wave changes is represented in table 1. Thirty-six of the patients (or 58 per cent) had coronary artery disease. Adding the other 16 patients with established cardiovascular disease, the incidence of heart disease among patients exhibiting a positive postextrasystolic T-wave change is 84 per cent. The only patient in this group diagnosed as having functional heart disease was an 82 year old man with generalized arteriosclerosis. At the time of recording these changes in the T wave three of the patients were having gastrointestinal hemorrhages; in two of these the hemorrhages were exsanguinating and the postmortem examination showed no coronary artery disease. One patient who showed electrocardiographic evidence extremely suggestive of myocardial infarction as well as a positive postextrasystolic T-wave change was found at postmortem to have a normal heart but a ruptured aneurysm of the circle of Willis. Five lacked definite evidence of heart disease; four of these patients, however, had hypertension and one had long-standing bronchial

Table 1.—*Clinical Features in 62 Patients With Positive Postextrasystolic T-Wave Changes*

Etiologic background	Number
Recent or old myocardial infarction	27
Definite angina pectoris without infarction	6
Probable angina pectoris	3
Diffuse myocardial fibrosis at postmortem	1
Hypertensive heart disease without angina pectoris or infarction	13
Syphilitic heart disease	1
Rheumatic heart disease with congestive heart failure	1
Gastrointestinal hemorrhage with normal hearts	3
Functional heart disease	1
Ruptured aneurysm of circle of Willis	1
Questionable heart disease	5
Total	62
Age range	47–85 years
Mean age	62
Sex distribution	Males 50 Females 12

FIG. 1. *Clear-cut "coronary" type postextrasystolic T-wave changes in a 58 year old man with an old anteroseptal infarct.* In this case the changes were pronounced in leads V_3 and V_4, less striking in the other precordial leads, and not apparent in the extremity leads. The late "coronary" type of T-wave inversion here suggests predominantly subepicardial changes.

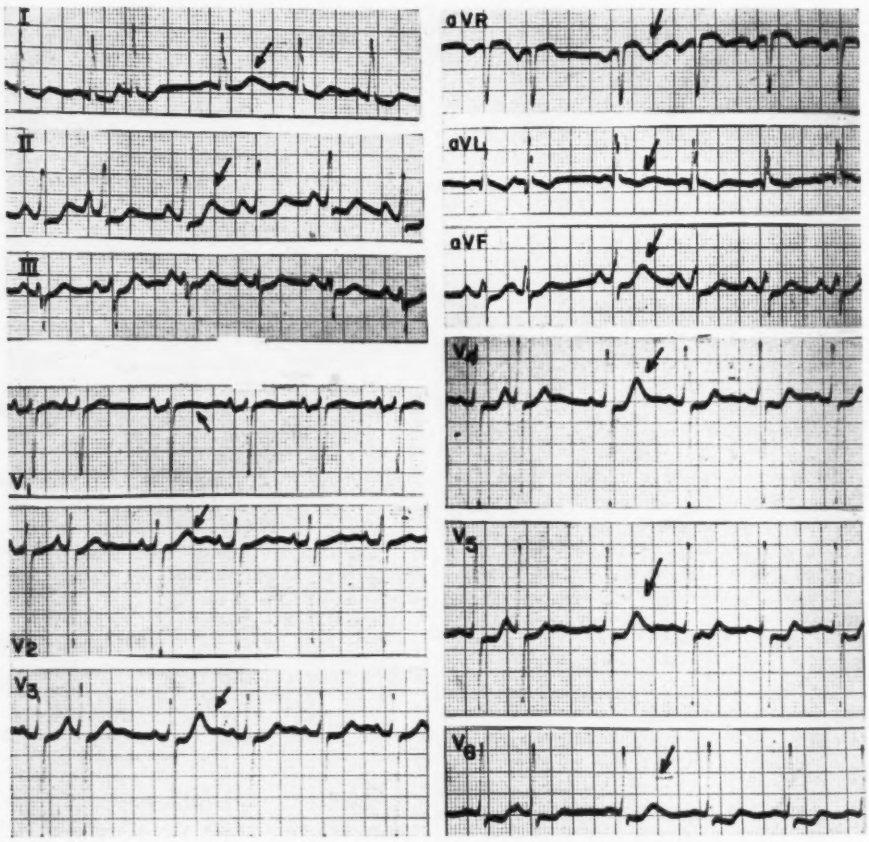

FIG. 2. *Postextrasystolic T-wave changes of "subendocardial" type present in all extremity and chest leads studied.* Such widespread changes are unusual. The patient was a 50 year old man with severe hypertensive heart disease and angina pectoris. Master test positive. The premature beats were auricular in origin.

asthma. In the majority of cases a positive postextrasystolic change is therefore correlated with convincing evidence of heart disease. The great preponderance of the male sex and the mean age of 62 years further reflect the predominant background of coronary artery disease in this population.

In 25 of the 62 patients premature beats were frequent enough to be present in all or most of the 12 leads recorded. This permits a

statement of the topographic distribution of the positive postextrasystolic T-wave changes. In 16 of the 25 the changes were predominantly

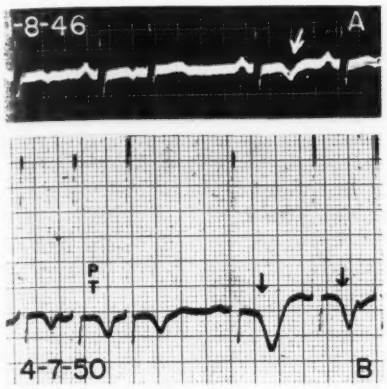

FIG. 3. *Postextrasystolic T-wave changes following auricular premature beats recorded in same individual over a four-year period.* (*A*) Lead II recorded January 8, 1946, showing an auricular premature beat with ventricular aberration; T-wave inversion in postextrasystolic beat. (*B*) Lead V_4 recorded April 7, 1950, showing paired auricular premature beats. Note profound T-wave deepening in the two beats after the pause. The patient was a 51 year old artist with hypertensive heart disease and chronic alcoholism.

chest leads. This tendency to specific spatial orientation around position V_3 or V_4 suggests a disturbance in the myocardial zone supplied through the descending branch of the left coronary artery. Another aspect of the topography of this T-wave change is its distribution with reference to the subepicardial and subendocardial laminae of the ventricular wall. More than two thirds of the patients showing positive postextrasystolic change had a "subepicardial" type of change in the sense of a decreased height or terminal or total inversion of the T wave. The association of these changes with prolongation of the Q-T interval frequently produced the characteristic appearance that has been designated as the "coronary contour" (fig. 1). The remaining third of the cases showed a "subendocardial" type of change, namely, depression of the RS-T segments (fig. 2), less pronounced inversion or increased amplitude of the T waves.

Occasionally when the extrasystoles were paired the T waves were altered in the two beats following the pause (figs. 3*B* and 4) or only in the second beat following the pause (fig. 5). At times T-wave changes were present

FIG. 4. *Postextrasystolic changes following paired or interpolated premature beats.* T-wave inversion in two beats following paired ventricular premature beats. The patient was a 68 year old man with angina pectoris. Master test positive.

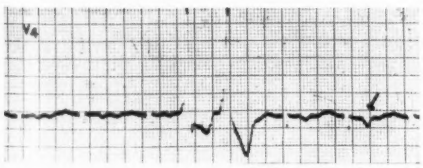

FIG. 5. *T-wave changes in second beat following paired ventricular premature beats.* A short pause precedes first postextrasystolic beat, long pause precedes second postextrasystolic beat.

or exclusively recorded in the precordial leads (generally leads V_3 and V_4), in four in the limb leads and in five cases both in the limb and in a series of postextrasystolic beats following single or repetitive premature beats and gradually or abruptly resumed a normal appearance. This phenomenon is somewhat reminiscent of the transient T-wave changes which may continue for hours, days or weeks, following a paroxysm of tachycardia (the so-called post-tachycardial syndrome).

In two instances positive postextrasystolic T-wave changes were associated with left bundle branch block. Generally the existence of left bundle branch block obscures evidence of concomitant myocardial damage since these

changes are lost in the electrocardiographic changes produced by the left bundle branch block itself. The presence of positive postextrasystolic T-wave alterations may, in these instances, offer otherwise unobtainable evidence of myocardial impairment.

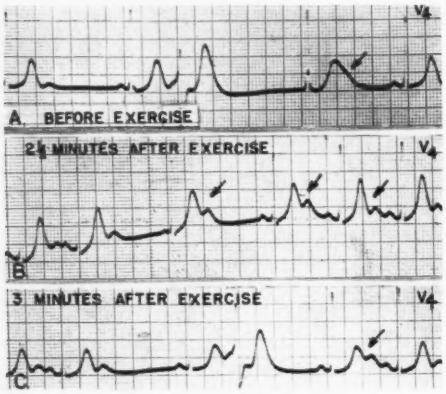

FIG. 6. *U-wave changes in beats following long pauses.* (*A*) Lead V_4 immediately before exercise. Note appearance of broadening of T wave (arrow) in postextrasystolic beat due to incorporation of U wave in latter half of T wave. The premature ventricular beat arises at the apex of a U wave. (*B*) Lead V_4 two and a half minutes after exercise. Note that in the third and fourth beats, which follow long pauses (the third beat is an escape beat), the U wave rides up on the descending limb of the T wave. In the beats following shorter pauses the U wave arises almost at the isoelectric line. (*C*) Lead V_4 three minutes after exercise. Premature beat has onset at apex of U wave. The U wave of the succeeding postextrasystolic beat again arises on the descending limb of the T wave.

TABLE 2.—*Clinical Features in 77 Patients with Negative Postextrasystolic T-Wave Changes*

Etiologic background	Number
No cardiovascular disease	35
Functional heart disease	11
Questionable heart disease	10
Hypertension	5
Hypertensive heart disease	11
Rheumatic heart disease	1
Myocardial infarction	4
Total	77
Age range	14–87 years
Mean age	47
Sex distribution	Males 42 Females 35

In a small number of cases changes in the postextrasystolic T wave were associated with changes in the U wave of the same ventricular complex. While the T wave of the postextrasystolic beat in some cases diminished in amplitude, the U wave became taller, producing in effect a broad, notched T wave. The electrocardiograms reproduced in figure 6 were recorded in a 57 year old woman undergoing a Master test. The upper strip (fig. 6*A*), taken before exercise, shows an apparent increase in the T-wave area after a premature beat. This results from the incorporation of a U wave in the T-wave area. The escape beat following a sinus pause in the next strip recorded two and one-half minutes after exercise (fig. 6*B*) shows no apparent change in the T wave but the U wave "rides up" on the downstroke of the T wave. In the third strip (fig. 6*C*) a similar U wave was in the process of being inscribed on the downstroke of a T wave following sinoauricular block, but this was interrupted at its apex by the beginning of a ventricular premature beat. Similar incorporation of a U wave in the T wave has been observed in another patient following a short bout of paroxysmal tachycardia.

B. Incidence and Significance of Negative Postextrasystolic T-Wave Changes

The over-all results in this group of 77 patients are shown in table 2. A negative postextrasystolic T-wave change was observed in four patients who had survived myocardial infarctions. In 12 other patients with cardiovascular disease the postextrasystolic T waves showed no changes. Thus 16 (or 20.8 per cent) of the 77 patients in this group had definite heart disease. This group without postextrasystolic changes differs from the first group in that the mean age was 15 years younger and in that there was no significant male sex predominance. This may be a reflection of the relative absence of coronary artery disease in the group with negative postextrasystolic T-wave changes.

To explore further the possible value of the postextrasystolic T-wave alterations, a group

of patients was investigated whose cardiac disturbance was regarded as functional. Such patients frequently tax the acumen of the clinician; numerous tests may be necessary before a final diagnosis can be established. If the T wave after a compensatory pause offers, in a positive or negative way, evidence of the status of the myocardium, it might be of particular value in this group of patients. Table 3 shows the over-all results for the 62 patients believed to have functional heart disease. By the criteria enumerated above only two patients (or 3 per cent) had positive changes. One of these patients was an 82 year old man. The other was a 62 year old woman whose chest pain at times came on with effort; early anginal discomfort could not be excluded. It would seem then that a positive postextrasystolic change is rare in the absence of heart disease. In its mean age and sex distribution this group of patients with functional heart disease was similar to the group without T-wave changes following premature beats (that is, negative postextrasystolic changes).

C. Relation of Postextrasystolic T-Wave Changes to Results of Master Two-step Test

The results of the relation of postextrasystolic T-wave changes to the Master test are shown in table 4. In 92 per cent of the 26 patients studied the two technics coincided, that is, a positive postextrasystolic T-wave change coincided with a "positive" Master test (fig. 7) and a negative postextrasystolic change corresponded to a "negative" Master test. The only patient with a positive postextrasystolic change and a negative Master test had typical angina pectoris of effort; the two patients with positive Master tests and negative postextrasystolic T-wave changes also had the characteristic symptoms of angina pectoris. This experience, limited though it is, none the less suggests that an extrasystole, or the pause following it, may induce a derangement in repolarization in an already injured myocardium which is comparable in its significance with the electrical alterations induced in the same heart by exercise.

Discussion

These studies point up a high degree of correlation between the presence of positive postextrasystolic T-wave changes and clinical evidence of significant heart disease and, to a lesser extent, the absence of such changes when clinical evidence of heart disease is not demonstrable. The criteria of "positivity" here employed are arbitrary. The value of the standards evolved is that they provide an index for the existence of underlying heart disease comparable to that obtained from the currently employed two-step stress test. In an era of multiple, complex, expensive and, at times, even hazardous, laboratory procedures, it is worthy of emphasis that the interpretation of the postextrasystolic T-wave change is based on information already available in the routine electrocardiogram.

Table 3.—*Incidence of Positive and Negative Postextrasystolic T-Wave Changes in 62 Patients with Functional Heart Disease and Frequent Premature Beats*

Negative P.E.S.T.	44
Positive P.E.S.T.	2
Minor changes	16
Total	62
Age range	8–82 years
Mean age	43
Sex distribution	Males 33 Females 29

Table 4.—*Relation of T-Wave Alterations in Postextrasystolic Beat to Two-Step Master Test*

	Number	Positive Master test	Negative Master test
Positive P.E.S.T.	12	11	1
Negative P.E.S.T.	14	2	12

A conception of the mechanism of the changes in ventricular repolarization following premature beats must take the following possible factors into consideration: (1) changes in repolarization related to cycle length; (2) the effect of the particular occasion for the pause; (3) hemodynamic factors in the postextrasystolic beat; and (4) mechanical factors.

1. Changes in Repolarization Related to Cycle Length. It has been suggested by Ashman that the T wave of the normal human electrocardiogram has the same direction as the QRS complex because of local differences in the duration of the excited state, specifically because the rate of repolarization is slower in the subendocardial than in the subepicardial laminae of the ventricles. This is a physiologic phenomenon. Where there are such local differences in the rate of repolarization, giving rise to T waves having the same direction as the QRS complexes, experimental acceleration of the heart at more and more rapid rates eliminates these local differences in the rate of repolarization so that eventually the T wave has a direction opposite the QRS complex and an equal magnitude. It seems probable that somehow shortening the cycle length produces a greater shortening of repolarization in those parts of the ventricle where this process was originally longest. Having thus inverted the T wave by accelerating the heart, the preexistent local differences may now manifest themselves if the heart is slowed; the T wave then becomes upright again. Conversely, if the T wave is originally inverted, acceleration of the heart apparently produces a greater relative shortening of the excited state subepicardially, thus making the T wave upright, and slowing the heart produces reinversion of the T wave. A clear demonstration of this idea was published recently by Segers and co-workers.[2] A patient showed inverted T waves during the so-called "post-tachycardiac syndrome"; at this time postextrasystolic T waves were upright. Following recovery, when the regular T waves were upright, postextrasystolic T waves were inverted. Although, as will become clear, this conception is open to some objections, it does seem probable from experimental evidence that induced (for example, by carotid sinus stimulation) or spontaneous (for example, in the pause following extrasystoles) lengthening of the cardiac cycle may under certain circumstances unmask T-wave changes.

In those cases in which extrasystoles were recorded in varying degrees of prematurity, the postextrasystolic T-wave changes were more pronounced the greater the degree of prematurity. A number of cases were observed in the present study in which striking changes were present when the premature beats were early, but absent or equivocal when late. These observations accord with Scherf's view[3] that it need not be an extrasystole, nor whether the beat is an auricular, nodal or ventricular premature beat, but the length of the pause that in large part determines the change in the T wave. Scherf has recorded similar T-wave changes clinically in the beat following the long pause in blocked auricular premature beats and in partial auriculoventricular heart block while Scherf[3] as well as Grant and co-workers[4] detected such changes after the long pauses in auricular fibrillation.

2. The Effect of the Particular Occasion for the Pause. Although an explanation for these T-wave changes has been presented predicated upon changes in heart rate, and therefore of cycle length, this need not be the only explanation for such changes. In certain cases T-wave changes were found to be quite independent of heart rate. In a 66 year old man with angina pectoris, for example, inverted T waves were recorded in lead V_4 before exercise (fig. 7); the postextrasystolic beat in this strip showed a more deeply inverted T wave and a longer Q-T interval than the regular beats in this same lead. Yet in this same lead the T waves became upright immediately after exercise though the cycle length was very close to, or identical with, that before exercise. In this same patient moreover no changes were recorded in the T waves during the long cycles produced by carotid sinus stimulation or following a spontaneous sinus pause of duration comparable to a compensatory pause which, in the same lead, had been followed by T-wave inversion. Alzamora[5-7] found that by the alternative tests of exercise and of carotid sinus stimulation one can, in effect, "dissect" the T wave. Whereas exercise may cause inverted T waves to become upright, carotid sinus stimulation (or the postextrasystolic beat) tends to produce inversion of atypical (notched, flat, isoelectric or diphasic) T waves or deeper inversion of originally inverted T waves. In this way he was able to unmask occult T-wave changes in leads that originally showed atypi-

cal but not necessarily pathologic T waves. The present results are in general accord with those of Alzamora, but the fact that in about one third of the cases here reported the T wave following the pause became upright rather than inverted (figs. 2, 8*A*) suggests that the effect of the long spontaneous pause, no matter what its cause, is not necessarily identical

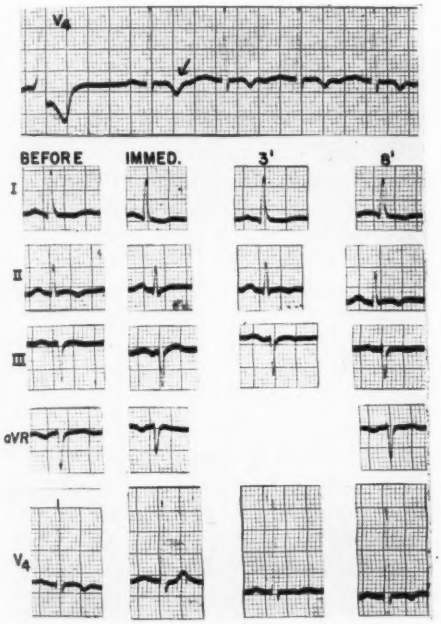

FIG. 7. *Postextrasystolic T-wave changes correlated with a positive Master test.* Note that the T wave of the first beat following the premature beat in the upper strip (lead V_4) is 2 mm. deeper and the Q-T interval 0.06 second longer than that of the regular beats in this lead. Immediately following standard exercise the T wave in lead V_4 showed a total reversal in direction from inverted to upright, then over the course of the next few minutes gradually returned to its original direction. The patient was a 66 year old man with angina pectoris.

with that induced by carotid sinus stimulation. Isolated observations in the present study suggest, as suspected by Scherf,[3] that the length of the pause is only one factor and that the occasion of that pause may also be a factor in producing these changes.

Meyer and Schmidt,[8] who found T-wave changes in the complexes after ventricular premature beats, found none in the postextrasystolic beats of five patients with auricular premature beats. They inferred from this that it must be an eccentric electrical activation of the ventricle that makes manifest a latent disorder in its repolarization. In view of the

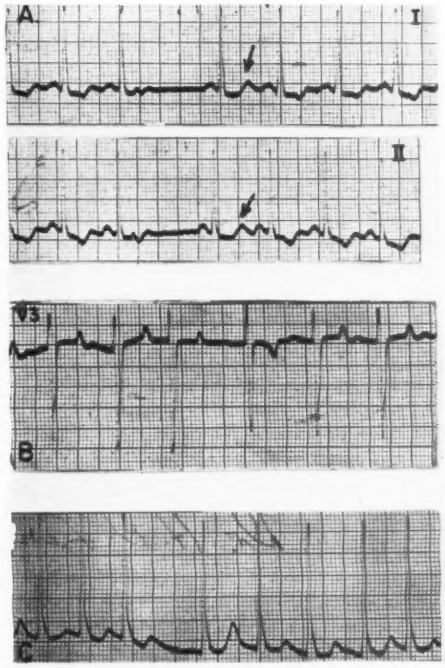

FIG. 8. *T-wave changes following pause with blocked or conducted auricular premature beats or auricular fibrillation.* (*A*) Change from an inverted T wave in the regular beats to a diphasic T wave in the beat following a pause resulting from blocked auricular premature beats (leads II and III). The patient was a 45 year old hypertensive brewer with possible cirrhosis of the liver. (*B*) Total inversion of T wave in beat following a conducted auricular premature beat recorded (lead V_3) in a 55 year old man with central nervous system and cardiovascular syphilis. No angina pectoris. (*C*) Change from diphasic to large upright T wave in beat following long pause in auricular fibrillation.

previous[3, 9] and present (figs. 2, 3, 8*B*) demonstration of T-wave changes following auricular premature beats, this view must be regarded as untenable.

3. Hemodynamic Factors in the Postextrasystolic Beat. In many communications upon

this subject there has been a tendency to relate these changes to alterations in cardiac dynamics attendant upon the greater cardiac filling associated with prolonged diastole.[3, 4, 9–11] This cannot in itself be an entirely adequate explanation else all individuals with extrasystoles might be expected to show this type of change. A possible extension of this principle may, however, explain why this change is more prone to occur in association with myocardial impairment. Johnston and DiPalma[12] have shown that there exists normally, at the height of mechanical systole, a difference of pressure in the various laminae of the ventricular wall, the pressure being greater in the deeper than in the more superficial layers. This pressure difference has been adduced to explain, in whole or in part, the normal difference between the deeper and more superficial layers in the duration of the excited state. Though no direct evidence upon this point is available, it is suggested that an exaggeration of these mechanical differences, due to the greater intracavitary pressure developing during prolonged diastole, produces, reflexly or directly, further restriction of coronary blood flow to the inner layers of the myocardium when there is already some actual or latent inadequacy of the flow. The electrical phenomenon of repolarization might thus be affected by the long pause. It should be noted that one must invoke a reverse explanation for those cases in which the direction of the T wave suggests exclusive or predominant impairment in the subepicardial laminae of the ventricle.

4. Mechanical Factors. Alternatively Grant, Estes and Doyle[4] ascribe T-wave inversion after long pauses in a case of auricular fibrillation to mechanical impact of the heart against the chest wall contingent upon the prolonged diastole of the filling period. Figure 8*C* in the present study, on the other hand, shows a taller T wave after such a pause; a mechanical subepicardial injury cannot explain this change.

Since the T wave may become inverted in a perfectly normal heart as the rate increases, and again become upright as the rate slows, it is theoretically reasonable that changes in myocardial repolarization, though empirically associated generally with evidence of myocardial impairment, need not necessarily indicate the latter.[13] The difference may be quantitative rather than qualitative. It is now well known, for example, that nervous influences such as sympathetic-parasympathetic imbalance[14, 15] may, in certain cases of neurocirculatory asthenia, be associated with T-wave changes which at one time were considered to be evidence of disease of the myocardium. In the 62 cases of "functional heart disease" here presented, two showed distinct T-wave changes in the postextrasystolic beats and 16 showed minor changes in T-wave voltage and/or the Q-T interval duration which we have arbitrarily considered as normal variations. Of further interest in this connection were the postextrasystolic T-wave changes recorded in the woman described above in whom postmortem examination showed a ruptured aneurysm of the circle of Willis but no myocardial infarct or coronary artery disease. The evidence at hand suggests, therefore, that postextrasystolic T-wave changes may in rare instances occur in the absence of disease in the myocardium proper.

Von Fernbach[11] reported postextrasystolic T-wave changes as a temporary phenomenon in two patients with myocarditis following tonsillitis. Although in the present study transient changes have been observed relatively infrequently in chronic rheumatic heart disease, it might be expected to be more frequent during acute rheumatic fever, at a time when, presumably, myocardial factors are of greater moment than mechanical valvular factors. The observation that angina pectoris may disappear following an acute myocardial infarct and that the anoxemia test may be positive more frequently in angina pectoris before than after an episode of myocardial infarction[16] suggests that the response to this test may vary with time; this has been explained as indicating that the patient may have regained an adequate collateral circulation. In a limited number of observations in the present study in which tracings were taken over a number of years, the tendency has been rather for a persistence of these changes. Figure 3 is an example of T-wave changes

following auricular premature beats on two occasions separated by over four years. It would seem possible, however, that similar transitory changes might occur in the postextrasystolic T waves of patients with coronary artery disease.

There is considerable confusion in the literature concerning the significance of simple changes in the duration of the Q-T interval of the postextrasystolic beat. It is not clear, for example, which of various criteria suggested[17-20] might serve as a yardstick enabling one to differentiate pathologic from physiologic prolongation of the Q-T interval. Indeed present experience coincides with that of Ashman[21] that there is a lag rather than a prompt adjustment of the Q-T interval to changes in cycle length, a fact which he has advanced to explain the absence of easily measurable changes in the T wave of the postextrasystolic beat in normal persons.

The U wave, whose significance is still unsettled, is commonly held to be related intimately to the process of myocardial repolarization and to coincide with the supernormal phase of myocardial excitability.[22, 23] The present evidence suggests that in certain cases alterations in the U wave may constitute an integral part of the postextrasystolic changes here described.

Summary and Conclusions

Pronounced "primary" changes may occasionally be detected in the voltage or direction of the T wave or in the duration of the Q-T interval of the beat following ventricular premature beats, following conducted or blocked auricular premature beats or following long pauses in auricular fibrillation. These changes are generally associated with coronary artery disease but may also occur in association with a wide variety of conditions producing profound permanent or transient myocardial impairment. It is possible that in rare instances they may occur in individuals with no detectable heart disease. Changes in the U wave may at times constitute an integral part of these postextrasystolic changes. The mechanism of these changes is not clear. Variations in cycle length are probably contributory but do not explain all the phenomena observed. The mechanical effect of overdistension of the ventricular wall in vulnerable hearts with selective local restriction of blood flow may be another factor.

It is concluded that the ventricular complex following a fortuitous lengthening of the cardiac cycle, however produced, is a convenient one to examine for T-wave changes. These alterations, when striking, suggest myocardial "ischemia" or "ischemia-like changes."

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Clinical Characteristics of Hypertension Associated with Unilateral Renal Disease

By GEORGE A. PERERA, M.D., AND ARTHUR W. HAELIG

A comparison has been made of 20 patients with unilateral renal disease, apparently cured of their hypertension by nephrectomy, and of another group of 20 who showed persistence of elevated blood pressure readings after surgery. Evidence is presented that unilateral renal disease, when it is responsible for hypertension, produces an acute, severe and accelerated process different in many respects from the usual picture of essential hypertension or of chronic bilateral renal disorders. The diagnostic value and the possible bearing of this observation on the mechanisms of renal hypertension are discussed.

IT IS now established that unilateral renal pathology may be responsible for hypertension in rare instances, as demonstrated by apparent cure following the removal of the kidney which is at fault. This subject, together with descriptions of the rigid criteria necessary before conclusions can be drawn, has been reviewed extensively.[1-3]

The clinical features of this form of elevated blood pressure have not received much attention. For this reason, certain characteristics of the disease picture have been investigated with the hope that they may prove of additional diagnostic value and throw some light on underlying mechanisms of renal hypertension.

CLINICAL MATERIAL

Several hundred records were examined, including most of the published literature dealing with hypertension due to unilateral renal disease. From this material, patients were selected from the literature, from the records of the Presbyterian Hospital and from private patient records, provided that they fulfilled certain criteria. Each subject, to be included in this survey, was required to have had definite hypertension (multiple readings above 140/90), adequate examination of the ocular fundi prior to surgery, and restoration of normal blood pressure readings (at least five values less than 140/90 after discharge from the hospital and remaining normotensive for a minimum period of observation of one year) following removal of a diseased kidney. Twenty such patients were found.

RESULTS

Some of the clinical data as well as the pathologic findings in the excised kidney are summarized in table 1. No patient in this group developed a clear-cut cerebral vascular accident and only one complained of cardiac pain, limited to a six months' period before but not after operation. Congestive failure, relieved by the surgical procedure, was clearly evident in but one instance, and was suggested in two additional cases by history alone. The findings on urinalysis were omitted intentionally from this study because of the obvious difficulty of relating abnormalities in the urine to vascular disease when their basis was primarily renal disease.

Twelve of the 20 patients, whose ages were scattered throughout seven decades, were male. None gave a story of antecedent hypertension of long duration. In 11 instances a normal blood pressure had been recorded within six years of the time of operation, and 10 of these were normotensive within four years.

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On at least one occasion, diastolic values of 130 or over were noted in 17 of the series. Infection was generally responsible for the disease found in the removed kidney.

In association with the hypertension which preceded surgery, moderate to severe headaches were apparent in three-quarters of the group, four developed convulsions, and 14 of the 20 showed definite retinopathy including hemorrhages, exudates or papilledema or a combination thereof. Of the six patients who failed to have significant retinal changes, high diastolic blood pressure values, of headaches and convulsions, of advanced retinopathy in almost all but young children, lends support to this concept. Furthermore, the conspicuously short history of illness suggests that the process is of a rapidly progressive nature from its incipiency.

In these patients in whom a causal relationship is established between hypertension and unilateral renal disease, it would thus appear that the usual clinical pattern is of an accelerated nature. Conceivably, however, many comparable subjects who exhibit a low-grade or "benign" course fail to reach the point of surgical intervention and hence have been excluded automatically from consideration. To answer this objection, the records were reviewed of 20 consecutive adult patients encountered in this clinic or seen in consultation who were believed to have had hypertension on the basis of unilateral renal disease but whose blood pressure failed to be restored to normal values following nephrectomy. The findings on funduscopic examination were

TABLE 1.—*Clinical and Pathologic Data in 20 Patients with Hypertension Related to Unilateral Renal Disease*

No. and Ref.	Sex	Preoperative											Pathology	Postoperative				
		Age			B.P.		Retinitis			Headaches	Convulsion	Card. Enlarg.		Followed (Yrs.)	B.P.			
		Last Normal B.P.	On Diag. Hypertension	At Op.	Systolic Range	Diastolic Range	Hem.	Exud.	Papilledema						Systolic Range	Diastolic Range	No. of B.P. Readings	Residua
1[4]	M		2½	2½	150–200	106–134	0	0	0			+	Pyelonephritis	3	92–120	62–75	5	0
2[5]	M		3	6	145–175	85–120	0	0	0			+	Partial arterial occlusion	3	92–122	50–76	21	Slight card enlargement
3[6]	M		6	6	145–240	90–140	0	0	0	+	+	0	Pyelonephritis	1½	80–100	40–80	12	0
4[7]	M		7	7	130–200	98–170	0	0	0	+	Loss of consc.	+	Hydronephrosis	1	90–110	60–90	7	0
5[8]	F	3	6	7	170–225	110–178	+	+	+	+		+	Pyelonephritis	5	102–110	70–83	6	Retinal scars
6[9]	F		19	19	175–230	125–150	0	0	+	0	0	?	Nephrosclerosis	3	140/85 or less		±36	0
7[10]	F		20	21	210–240	120	0	0	+	+			Pyelonephritis	2	110–122	72–82	5+	0
8	F		23	23	130–245	80–145	+	+	+	0	0	+	Nephrolithiasis	5	110–146	70–86	6	0
9	M	25	27	27	194–220	118–150	+	+	+	+	0	0	Pyelonephritis	2	100–126	60–82	10+	0
10[11]	M		32	32	150–210	114–130	+	+	+	+		0	Multiple infarcts	2	120–124	78–84	8	0
11[12]	F	35	35	35	160–180	90–110	0	0	0	+			Arterial obstruction	1½	110–120	70–80	9	0
12	M	32	35	35	190–250	128–160	+	+	+	+	0	0	Tuberculosis	3	104–136	70–86	15	0
13[13]	F	35	36	37	160–220	90–130	0	0	0	+	0	0	Pyelonephritis	2	110–140	70–90	12	0
14[13]	M	41	42	43	220–224	120–165	+	0	+	+	+	+	Pyelonephritis	2	115–148	75–85	12	0
15[14]	M		41	43	230	120–130	+	0	0	+		+	Pyelonephritis	1½	±130	80–90	20+	0
16	M	50	56	56	160–190	124–146	+	+	+	+	+	?	Pyelonephritis	1	120–134	74–82	6	0
17	M	55	57	58	200–220	106–140	+	+	0	+	0	+	Arterial embolism	3	128–140	76–88	8	0
18	M	56	60	60	210–230	120–130	+	+	0	+	0	+	Pyelonephritis	5	130–140	60–80	10+	Retinal scars
19	F	58	60	60	160–220	100–140	+	+	+	+	+	+	Arterial embolism	1½	120–140	64–86	8	0
20	F	60	63	64	180–240	120–150	0	+	+	0	0	+	Pyelonephritis	7	120–140	70–86	10+	0

four were less than 8 years of age, and one adult had had hypertension only for a matter of days before surgical removal of a diseased kidney.

DISCUSSION

The present study affords considerable evidence that the hypertension associated with unilateral renal disease is not only severe in intensity but clinically of the accelerated or so-called "malignant" type.* The frequency of

* A suggestion first made to us by Dr. Paul Wermer of this institution.

recorded in 10 instances; not one showed a retinopathy. Thirteen gave a history of hypertension of more than four years' duration. In contrast to the series which responded by apparent "cure," diastolic values of 130 or over were recorded in but five of these 20 patients; only seven complained of headaches; and the renal pathologic diagnosis of pyelonephritis was made in only five instances as opposed to a high incidence of nephrosclerosis and congenital hypoplasia. Sensitization of the vascular system or changes in the opposite kidney could explain the failure of this group to respond but could not account for the more benign clinical course of these patients.

The observation that hypertension associated with unilateral renal disease is of an acute, severe and rapidly progressive type, deserves added confirmation. The evidence for it is sufficiently strong already to suggest that the presence or absence of such a pattern might be of diagnostic value in determining the likely candidates to respond to nephrectomy. As hypertensive vascular disease rarely if ever begins after the age of about 50,[15] the sudden appearance of a striking elevation of diastolic blood pressure in older age groups, known previously to have been definitely normotensive, should lead to the suspicion of another cause. The last seven patients in this clinic who developed hypertension abruptly after the age of 50 were shown subsequently to have sustained a unilateral renal insult (infection, vascular thrombosis or embolism) in every instance. All have responded to date to nephrectomy.

It is suggested also that these data may have some bearing on the problem of mechanisms. The accelerated phase is encountered in approximately 5 per cent of patients with essential hypertension;[15] retinal hemorrhages, exudates and papilledema develop in all combined phases of hypertensive vascular disease in 25 per cent at the most, and then only in terms of the total life history, certainly not as a rule in the first few years of the disease. Certain renal disorders, such as chronic glomerulonephritis or polycystic disease, exhibit generally a comparatively benign hypertensive course until kidney dysfunction becomes advanced. These comments suggest the strong possibility that the hypertension of unilateral renal disease is in some way different from hypertensive vascular disease, as well as from certain chronic kidney disorders, and is perhaps more closely related to the direct elaboration of a pressor substance against which no compensatory mechanisms have been established. Conceivably acute situations, such as acute glomerulonephritis and the divers factors which lead to acute urinary suppression (for example, carbon tetrachloride poisoning), fall into a similar category, but differ from unilateral renal disease in that patients either die promptly or recover completely.

The possibility must be entertained that some forms of experimental renal hypertension resemble the unilateral renal disease in man, whereas others give rise to a more chronic process on some fundamentally different basis. This should be taken into consideration before analogies are drawn between experimental data and human disease.

Conclusions

1. An analysis of 20 hypertensive patients with unilateral renal disease, apparently cured by nephrectomy, affords strong evidence that this condition gives rise to an acute, severe and accelerated type of hypertensive process.

2. This observation may be of diagnostic help and may serve to distinguish the patients likely to respond to nephrectomy.

3. It is suggested that the mechanisms involved in hypertension associated with unilateral kidney disease differ from those related to certain chronic bilateral renal disorders and to hypertensive vascular disease.

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Respiratory Variations in Blood Pressure

By A. C. Dornhorst, M.D., P. Howard, M.B., and G. L. Leathart, M.B.

A study of respiratory blood pressure variations in normal subjects suggests that variations in both cardiac output and peripheral resistance are involved, the latter mechanism being essentially similar to that producing the Traube waves in apnea. The interactions of the two mechanisms are compared to the known behavior of coupled electronic oscillators.

THE FLUCTUATION of the arterial pressure with respiration was first noted by Stephen Hales in 1733.[1] The subject has since attracted the attention of many workers and has a large literature. In spite of this there are, as we hope to show, aspects of this apparently simple and easily observed phenomenon which remain mysterious.

In this article we shall not attempt to review the literature. We shall summarize our experience as a series of propositions supported by illustrative records, merely indicating the relation of our views to received opinion. We shall then discuss the underlying mechanisms and describe some relevant experiments.

Material and Methods

Some 50 records of blood pressure and respiration, many with additional information, from normal volunteers and from patients with normal circulations, form the basic material of this report. All pressures were measured with capacitance manometers. Chest movements were recorded by a Manning spirograph operating either a capacitance or photoelectric pickup.

Results

1. *Abdominal and thoracic breathing have similar effects on the blood pressure* (fig. 1). The contrary view has often been expressed.[2] The disparity probably arises from a failure to standardize respiratory rate. Unless care is taken most subjects will breathe more deeply and more slowly with abdominal than with thoracic respiration.

2. *The amplitude of the blood pressure swings increases with decreasing respiratory rate* (fig. 2). This is generally agreed. We have found it to hold down to rates of about 6 per minute.

3. *The relation between the blood pressure variation and the respiratory phase is a function of respiratory rate.* At moderate rates the pressure is falling during most of inspiration. At slower rates inspiration is associated throughout with rising pressure. This rate dependence, which we have found very regularly, does not appear to have been widely recognized and may account for some conflicting statements made in the past. (fig. 3).

4. *Blood pressure swings are enhanced by the upright posture* (fig. 4). The enhancement is associated with an increase in the variation of pulse pressure. The left hand side of the figure shows that considerable pressure swings can occur with little change in pulse pressure.

5. *Sinus arrhythmia does not contribute to the blood pressure swings.* This statement is based on the frequent occurrence of an event illustrated in figure 4. Gross arrhythmia suddenly appears where there has been little change of heart rate in previous respiratory cycles: the pressure waves continue their course, the slowing being compensated for by increased stroke volume. When present, slowing always appears in the descending limb of the pressure wave, irrespective of the respiratory phase.

6. *During apnea regular pressure waves may occur* (fig. 5). These, which are conveniently called Traube waves,[3] are not associated with material pulse pressure changes unless, as sometimes happens, there is accompanying rate change, when the slowing on the descending limb is balanced by an increased pulse pressure. The waves are often fugitive, but when they occur their rate is consistently about 6 per minute.

7. *The blood pressure may exhibit fluctuations at a submultiple of the respiratory rate* (fig. 6). This phenomenon is quite common, but is not

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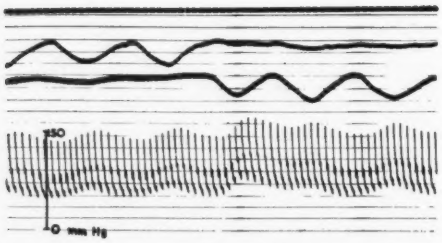

FIG. 1. From above downwards: time in seconds, thoracic spirogram, abdominal spirogram, blood pressure. The change from thoracic to abdominal breathing does not alter the phase of the blood pressure variations. In this and in all other figures inspiration corresponds to a downward movement of the spirogram.

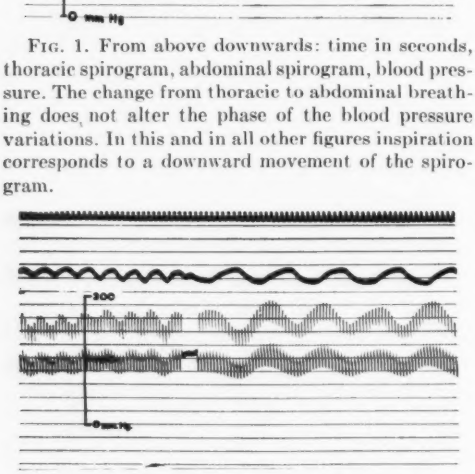

FIG. 2. Illustrating the effect of respiratory rate change on magnitude and phase of blood pressure swings.

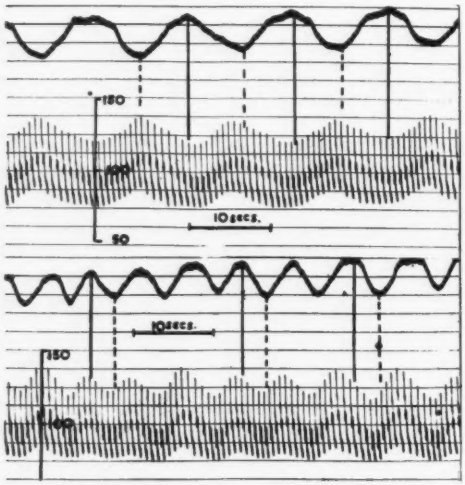

FIG. 3. Sections of a continuous tracing from an experiment in which the subject followed with his breathing a sinusoidal signal of slowly varying period. Between the fastest and slowest respiratory rates there is an almost complete reversal of the relation of blood pressure change to respiratory phase.

easy to investigate as it often disappears when a subject changes from unconsidered to deliberate breathing. Sinus arrhythmia may follow the slow wave rather than, or as well as, the respiratory waves.

FIG. 4. Two sections of a continuous tracing; the left hand one with the subject supine, the right hand one, erect. In the erect posture the fluctuations in pulse pressure are exaggerated. Sinus arrhythmia occurs from time to time and has little effect on the blood pressure waves.

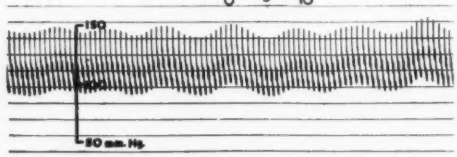

FIG. 5. Traube waves during apnea.

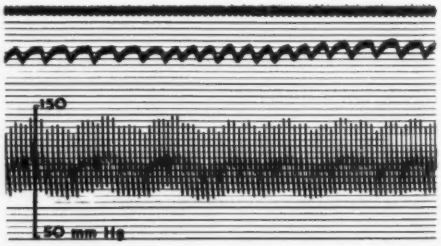

FIG. 6. In the above record there is a fluctuation at one third of the respiratory rate. The subject varies his respiratory rate from 15 per minute to 20 per minute and back. The slower waves maintain their relationship with the superimposed respiratory waves.

The slower waves are thus occurring at near the Traube (apnea) rate of 6 per minute but their frequency is entrained by variation in respiratory rate.

INTERPRETATION OF PRESSURE RECORDS

If the heart rate does not change, variations in peripheral resistance should produce corresponding variations in mean blood pressure with little change in pulse pressure, whereas

variations in stroke volume should produce variation in pulse pressure and mean pressure in about equal proportion. Conversely one may provisionally interpret pressure changes of the first type (equal systolic and diastolic swings) as indicating changes in peripheral resistance and changes of the second type (proportional systolic and diastolic swings) as indicating changes in stroke volume. Intermediate patterns may be attributed to the action of both factors, whose relative contributions may be to some degree assessed by noting the relation of pulse pressure to mean pressure modulation. For such an analysis, cycles with minimal rate variation must be selected. As will be seen later, the circumstances in which the pure patterns occur support these interpretations.

Mechanism of Stroke Volume Modulation

It is generally agreed that respiratory modulation of stroke volume is produced as follows. Inspiration lowers intrathoracic pressure and enhances filling of the right heart from the extrathoracic veins. Right ventricular stroke volume thus increases, and hence the effective (distending) pressure of the lesser circulation rises. The rise in effective pressure in the pulmonary veins leads to increased filling of the left heart and so to increased left ventricular stroke volume.

The dynamic implications of this mechanism have not, so far as we are aware, been recognized. It can be seen that the resistance and the hydraulic capacitances of the lesser circulation interpose a "lag" mechanism between inspiration and right ventricular output increase on the one hand and the rise of effective pulmonary venous pressure and left ventricular filling on the other. It follows that, for a given depth of respiration, stroke volume modulation will decrease with increasing respiratory rate. Moreover, while there is a primary phase relationship between inspiration and increased stroke volume, with increasing rates, the phase of the stroke volume change will lag increasingly behind the corresponding respiratory phase. It thus comes about that at moderately rapid rates stroke volume (and blood pressure) is falling throughout most of inspiration, the fall being due not to the accompanying inspiration but to the preceding expiration. The true causal connections may be displayed by interrupting breathing for a few seconds at different points in the cycle (fig. 7).

Stroke volume modulation is seen in its purest form when autonomic activity has been blocked by, for example, tetraethylammonium (fig. 8). The relationship between stroke volume change and chest expansion is inverted by passive lung inflation, and the dependence of the stroke volume on thoracic pressure rather than thoracic posture is thus confirmed (fig. 9). The enhancement of stroke volume modulation by the assumption of the upright posture, which is known to lower right auricular pressure, suggests that the relationship between right ventricular output and effective filling pressure is not a linear one but is steeper when the filling pressure is low.

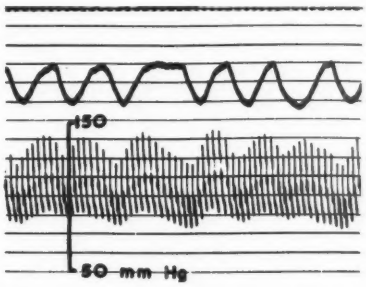

Fig. 7. An interpolated expiratory pause demonstrates that the fall of pressure accompanying inspiration does not depend on it but on the preceding expiration.

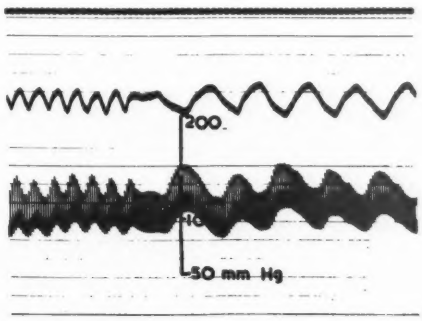

Fig. 8. Respiratory effects during tetraethylammonium blockade. There is no rate change and systolic and diastolic pressure changes are proportionate. For example, during the first slow wave systolic and diastolic pressures both increase 25 per cent. This probably represents pure stroke volume modulation.

Changes of intrathoracic pressure, acting as they do equally on pulmonary veins, left auricle and left ventricle, cannot immediately modify the existent intravascular pressure gradients between these regions, and no immediate effect on left ventricular filling is to be expected. Nevertheless, the first one or two beats accompanying inspiration after an expiratory pause often show a small but definite reduction

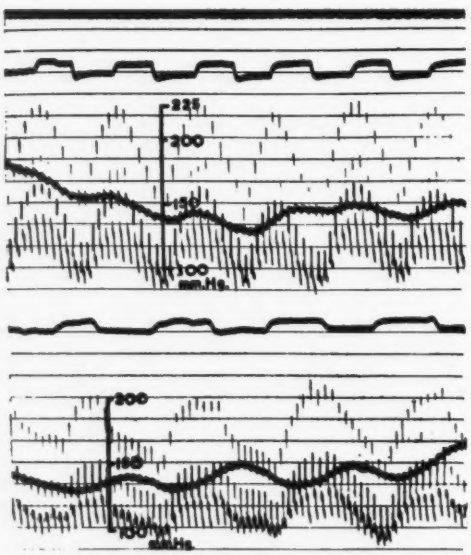

FIG. 9. Upper section voluntary breathing: lower passive lung inflation. The voluntary breathing pattern was deliberately matched to the inflation pattern. A parallel experiment showed that the relationship between intrathoracic pressure and thoracic posture was inverted during inflation. Active inspiration is followed by increasing, inflation by decreasing, pulse pressure. The trace overlying the blood pressure records hand volume: during passive deflation the hand shrinks in spite of rising blood pressure.

of pulse pressure before the expected increase occurs. This is because ventricular events are not wholly independent: since there is some sharing of the ventricular muscle the increased filling of the right ventricle at the start of inspiration tends to be at the expense of the filling of the left. This effect is always trivial in the normal but becomes important in cardiac tamponade. It is discussed in more detail elsewhere.[4]

MECHANISM OF PERIPHERAL RESISTANCE MODULATION

There is little doubt that the sympathetic nerves constitute the efferent pathway, and our experience is that it is blocked by tetraethylammonium but not by atropine. The purest form of this type of pressure variation is the Traube wave occurring in apnea (fig. 5). However, large respiratory variation in a supine subject often appears to depend more on resistance than on output modulation (figs. 1, 3, and 4a), and analysis of the records suggest that resistance changes usually play some part in the more conspicuous swings. The two influences are in general timed to reinforce each other (fig. 4). The question immediately arises how this synchronization is brought about. There is no shortage of possible synchronizing influences: for example, impulses might radiate from the respiratory to the vasomotor center, or might arise in lung stretch or other receptors sensitive to respiratory movements. In the first case, passive ventilation by lung inflation should abolish the synchronization, while in the second, it should invert the relationship between stroke volume and resistance changes. We have performed a number of experiments with passive lung inflation and while we have consistently produced the expected reversal of stroke volume modulation, the effects on the resistance changes have been less clear-cut as the blood pressure patterns have tended to be unstable (fig. 9). On the whole the results do not support the idea that lung stretch or similar receptors supply the sole "keying-in" stimulus.

Synchronizing impulses might also arise from receptors anywhere in the vascular system between the venae cavae and the carotid sinuses. Those near the right heart would tend to maintain the relationship between resistance change and respiratory phase; those near the left heart that between resistance change and stroke volume change. Since the two changes tend to reinforce each other the latter arrangement would imply that the baroreceptors were acting at certain frequencies not as a stabilizing negative feedback but as a positive feedback mechanism. This is made unlikely by the following observation. Sudden digital compression

of both femoral arteries causes a rise in brachial pressure of 5 to 10 mm. Hg. Rhythmic compression and release of the arteries over a wide range of repetition rates failed to evoke any regenerative effects in the three subjects tested.

Figure 10 shows the effect of short isolated inspirations and expirations (square-wave breathing). Since whether expiration is followed by constriction or dilatation depends on the repetition rate, it appears that the connection between resistance change and respiratory act cannot be a simple one.

One must conclude that the nature of the interaction between respiration and peripheral resistance remains obscure. However, it is worth attempting to describe succinctly the over-all action of the system.

Formulation of the Over-all Action

The following is an attempt to frame a general viewpoint conformable with the facts.

There exists a mechanism tending to produce rhythmic waxing and waning of vascular tone at a rate of around six a minute. This mechanism we may call the "Traube oscillator." For our present purposes it is immaterial whether this is, as suggested by Guyton and Harris,[5] a feedback oscillator or whether the rhythm is dependent on some quasi-autonomous pacemaker in the nervous system. We postulate some form of loose coupling between respiratory events and this oscillator so that the oscillator frequency is entrained by the respiratory rate. When the latter is near the "free running" oscillator rate of 6 per minute the magnitude of the oscillation is greatest: as the rate moves away the magnitude decreases along some sort of resonance curve. At fairly remote rates the subharmonic nearest to the free running rate may appear. This in its turn may be entrained over short ranges (fig. 6). The type of behavior here described is well recognized in coupled electronic oscillators[6] and although the analogy may seem farfetched it is difficult to see how any simpler one will explain, for example, the happenings in figure 6.

Thus at rates of, say, 20 a minute, respiratory variation is small and what there is is largely due to stroke volume modulation. As the rate slows the stroke volume modulation increases (and the phase lag decreases) as explained above. Simultaneously the contribution of peripheral resistance modulation increases as the Traube frequency is approached. A normal subject achieves maximal blood pressure swings by breathing at 6 per minute in the upright posture. He thus produces a large stroke volume modulation and reinforces this by resonating the Traube oscillator.

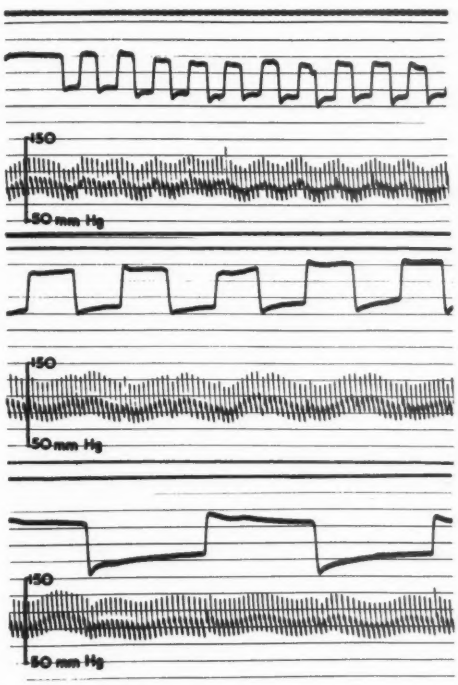

Fig. 10. The effect of "square-wave" breathing at different frequencies. Small transient spikes are seen at the moment of expiration: they are due to direct transmission of the intrathoracic and abdominal pressure impulse to the arterial system.

Familiarity with the normal behavior is obviously necessary for the early recognition of abnormal patterns of respiratory blood pressure variation, for example, pulsus paradoxus,[4] and it was with this aim that this study was undertaken. We suggest that the results have an additional interest as indicating the complexity of circulatory interactions and the scope for further work in apparently simple phenomena.

SUMMARY

The normal behavior of the respiratory blood pressure variations with alterations of respiratory rate and pattern, and of posture is described.

An analysis of the results suggests that variation in stroke volume and in peripheral resistance both contribute to the larger swings of pressure.

The mechanisms are discussed in the light of some simple experiments and a formulation of the general pattern of their interaction is attempted.

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Studies of Hemodynamic Changes in Humans Following Induction of Low and High Spinal Anesthesia

I. General Considerations of the Problem. The Changes in Cardiac Output, Brachial Arterial Pressure, Peripheral and Pulmonary Oxygen Contents and Peripheral Blood Flows Induced by Spinal Anesthesia in Humans Not Undergoing Surgery.

By Salvatore M. Sancetta, M.D., R. Beverley Lynn, M.D., Fiorindo A. Simeone, M.D., and Roy W. Scott, M.D., with the technical assistance of Gladys Heckman, R.N., and Hanna Janouskovec, R.N.

After a lapse of some years, surgeons and anesthesiologists alike are re-exploring the use of high spinal anesthesia, which is designed to produce a "useful" hypotension coupled with maximal relaxation. In the present study the hemodynamic changes induced by low and high spinal anesthesia, the latter arbitrarily defined as ablation of sympathetic, sensory and somatic nerves fibers above the fourth dermatomic segment, have been investigated in a series of waking patients not undergoing surgery.

SINCE the introduction of spinal anesthesia 54 years ago, no method of anesthesia has had a more controversial course. Some investigators have found it applicable to surgery on any part of the body,[12, 16, 24, 25, 46] while others[7, 28] place strict limitations upon the level of anesthesia for which it is safe, and also restrict its use to carefully selected patients. Surgeons and anesthesiologists alike have objected to the hypotension which often accompanies this type of anesthesia, especially when high levels of anesthesia are reached. In recent years, however, this very property of high spinal anesthesia has been offered as an advantage[12, 16] in that it provides the surgeon with excellent relaxation of the patients and permits an operation with virtually no blood loss. Since it seemed apparent that this technic would gain in popularity, it was thought advisable to evaluate the cardiovascular effects of hypotension induced by its employment in patients undergoing surgery[26] and in others not undergoing surgical intervention.

This report deals with the hemodynamic and blood oxygen content changes in 10 patients, five of whom were given low and five high spinal anesthesia, and in whom no surgical procedure was performed.

Material and Methods

Ten hospitalized patients were studied, six males and four females. The average age was 51.4 years. At first patients were excluded who showed evidence of cardiovascular disease on the basis of history, physical examination and electrocardiography. Subsequently, some subjects were included who showed evidence of mild heart disease or of healed cerebrovascular accidents. The majority of patients had varying degrees of anemia and pulmonary emphysema. The lowest hemoglobin level encountered was 8.8 Gm. per 100 cc. None had azotemia and the majority had normal bromsulfalein retention.

The conventional 12 lead electrocardiogram was recorded pre-operatively, during the spinal anesthetic, on the same afternoon as the investigation, and daily thereafter for seven days, when possible,

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in all patients. Precordial leads were not obtained during the period of anesthesia. All patients had a regular sinus rhythm.

On the evening before the tests, the patients received 1.0 Gm. of chloral hydrate orally. On the morning of the examination, 0.1 to 0.2 Gm. of sodium pentobarbital was administered orally. The patients were then transferred to the cardiovascular laboratory which was maintained at a temperature of 23 to 24 C.

The right side of the heart was catheterized with the standard Cournand type single lumen 7F catheter. The latter was introduced and kept in the pulmonary artery for the duration of the studies. The "zero" point for reference was taken to be 10 cm. from the posterior surface of the thorax. The peripheral arterial pressure was recorded through a number 19 indwelling intra-arterial needle introduced into the brachial artery of the same arm used for the cardiac catheterization. Pressures were transduced through Statham strain gauges and recorded by the Brush multichannel oscillograph.[47]

The baseline cardiac outputs were determined in duplicate according to the direct Fick principle, after a rest period of 30 minutes following introduction of the cardiac catheter and the intra-arterial needle. The volumes of expired air were measured through a gas test meter. Five minute samples were collected in Douglas bags. The oxygen content of room and expired air was measured on the Pauling oxygen analyzer after passage through a drier. All values were corrected to 0 C. and 760 mm. of Hg. The hematocrit levels of simultaneously drawn and heparinized specimens of brachial and pulmonary arterial blood were determined by the Wintrobe method.[45] Blood oxygen contents were determined by means of a previously standardized Beckman DU spectrophotometer.[20] The blood samples were obtained simultaneously from the pulmonary and brachial arteries. The specimens were collected by means of heparinized Luer-Lock syringes air-sealed with Aquaresin,* and immediately placed on ice. All determinations were done in duplicate. As an added control, direct arteriovenous oxygen differences were determined for simultaneously drawn samples of blood.

Mean auricular, pulmonary and brachial arterial pressures were calculated by the planimetric integration of the area under the recorded pressure curves over a period of two successive respiratory cycles. The total peripheral resistance was calculated according to the standard dyne formula:

$$T.P.R. = \frac{\textit{Mean systemic blood pressure}}{\textit{Cardiac Output}} \times 1332,$$

where pressure is expressed in millimeters of Hg, cardiac output in cubic centimeters per second, and 1332 is the conversion factor to reduce T.P.R. to dynes per second per cm.$^{-5}$, in terms of absolute units.[44]

Left ventricular work was calculated according to the formula:

$$L.V.W. = 0.0135 \times \textit{cardiac output} \times \textit{mean systemic blood pressure},$$

wherein the cardiac output is expressed in liters per minute, the mean arterial blood pressure in millimeters of Hg, and left ventricular work in kilogram meters per minute. The existence of basal cardiac outputs within the normal range and the directional changes in the brachial arterial pressures and in the cardiac outputs to lower levels, validates this estimation in the face of the inability to account for the kinetic factor in the formula:

$$L.V.W. = (0.0135 \times C.O. \times B.P.) + \frac{(mv)^2}{2}.$$

Peripheral blood flows and pulse volumes were measured by means of the Grass oscillographic plethysmograph,* employing air transmission through Grass and Statham strain gauges. The finger oncometer was placed on the index finger of the noncatheterized extremity, and simultaneous pulse volumes were determined on the second toe of either foot. The oncometers were sealed with Kal-Kord to the digits. When blood flows were estimated, an occlusion cuff was placed at the base of the digit and venous occlusion obtained by inflating the cuff from a pressure tank. The blood flows were expressed in cubic centimeters per 10 cc. of digit per minute and the pulse volumes in cubic centimeters per 10 cc. of digit.

After the control data had been obtained, the effects of spinal anesthesia were studied. Low spinal anesthesia, arbitrarily determined to be below the level of T-4, was induced by injecting 75 to 175 mg. of procaine slowly into the subarachnoid space at the level of the third or fourth lumbar interspace. High spinal anesthesia, determined to be above the level of T-4, was attained by injection of 150 to 175 mg. of procaine into the subarachnoid space, rapidly and with barbotage. In all cases of high spinal anesthesia there was a release of vasomotor tone in the finger, as against a vasoconstriction in low spinal anesthesia. In all instances a period of 15 minutes was arbitrarily taken as the time necessary to ensure proper fixation of the anesthetic. Vasoconstrictor drugs were not used with either low or high spinal anesthesia, despite the development of hypotension.

The cardiac output and the pressures in the brachial and pulmonary arteries were recorded 30 and 60 minutes after the administration of the spinal anesthetic. Right auricular pressures were recorded

* Glyco Products Co., Inc., 26 Court St., Brooklyn, N. Y.

* Grass Instrument Co., Quincy, Mass.

gain at the end of the 60 minute period when the ardiac catheter was withdrawn.

The results to be reported below will be confined o the general hemodynamic and blood oxygen hanges developing during low and high spinal nesthesia. The results of individual organ studies ill be presented in later communications.

Results

1. Mean Brachial Arterial Pressure. The mean brachial arterial pressure fell significantly in both groups of patients. The low spinal group showed an average reduction of 21 per cent from the basal level, and the high spinal group a reduction of 44 per cent. The systolic and diastolic pressures dropped proportionately, and when the former decreased to circa 90 mm. of Hg in normotensive patients, the pulse pressure was definitely diminished.

2. Cardiac Output and Index. These decreased in a manner similar to the blood pressure. In the low spinal group the maximal average reduction in the cardiac output was 16.2 per cent, and in the high spinal group it was 31 per cent from the basal level. The cardiac indices followed closely. Although the reduction in the blood pressure and the cardiac index showed a gross relationship, the trends of the two were not always parallel (fig. 1). In one patient (G. T.) who was given a low spinal anesthetic, there was no significant change in the cardiac output. This was the only patient who showed a minimal rise in blood pressure. In one patient who was given a high spinal anesthetic (F. D.) there was a transient fall and then a terminal rise in the cardiac output in spite of a profound decrease in arterial pressure. This remains unexplained.

3. Heart Rate and Stroke Volume. The heart rate decreased in all patients with the exception of one who experienced a small and transient rise (P. P.). There was an average maximal decrease of 8 beats in the low, and 10.8 beats in the high spinal group. The heart rate uniformly falls in the basal conscious patient under spinal anesthesia, following stabilization, in the absence of physical or psychic stimulation, and when vasoconstrictor drugs are not employed. The changes in the stroke volume reflected those of the cardiac output. In the low spinal group the stroke volume showed a small average decrease from 73.1 cc. to 68.0 cc., whereas in the high spinal group the reduction was more marked (57.0 to 43.5 cc.).

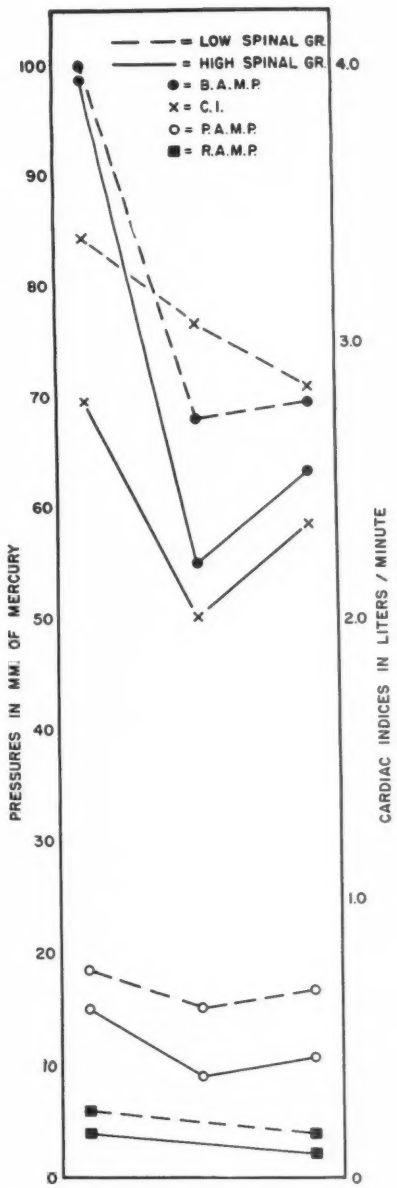

Fig. 1. Low and high spinal anesthesia. Average changes in cardiac index, brachial arterial mean pressure, pulmonary arterial mean pressure and right auricular mean pressure. Values for control, 30 and 60 minute determinations.

TABLE 1.—*The Hemodynamic and Blood Oxygen Changes Induced by Low Spinal Anesthesia*

Patient	Age	Sex	Diagnosis	Anesthetic & Level mg.	Brachial Arterial Pressure (mm. of Hg)			Right Auricular Pressure (mm. of Hg)		Pulmonary Arterial Pressure (mm. of Hg)		
					Control	30 min.	60 min.	Control	60 min.	Control	30 min.	60 min.
L. S.	46	M	Diabetes	Procaine 100	121/67	98.5/51	98.8/48	6.4/2.3	4.5/0	25.1/8.7	21.4/7.2	22.5/6.5
				T-4	87.0	69.5	67.0	4.55	3.42	17.3	14.9	15.8
N. W.	56	F	Coronary H.D. hyperthryoidism	Procaine 100	153/60	138/52	155/70	Bigeminy	16.4/6.2	49.7/18	44.2/14	50/18
				T-6	98.0	86.4	100	19.0	12.3	32.0	27.2	32.0
G. T.	46	M	Hepatitis	Procaine 75	120/66	126/72	132/78	4.0/0.1	3.7/−1.1	19.6/8.2	16.6/8.9	15.3/8.6
				T-11	93.0	97.0	102.0	1.94	1.08	13.9	12.4	12.6
P. P.	45	M	Chronic alcoholism	Procaine 175	136/84	97/64	101/64	3.0/−0.3	2.0/0.0	20.0/8.5	12.5/5.7	15.0/6.2
				T-4	107.0	77.0	80.0	1.6	1.2	12.8	8.2	10.0
T. D.	75	M	Bronchogenic carcinoma	Procaine 100	177/90	90/52.2	80.4/46	6.2/−0.5	1.7/−1.0	24.8/11.3	20.6/8.7	19.9/8.7
				T-4 and 5	115.9	65.8	63.3	2.83	1.05	16.1	13.5	13.5
Averages.....	53.6		—	—	100.2	79.1	82.5	5.98	3.81	18.4	15.2	16.8
Percentile Change.....			—	—	—	−21.0	−17.6	—	−36.3	—	−17.4	−8.7

Finger Blood Flow (cc./10 cc. part/min.)			Finger Pulse Volume (cc./10 cc. part)			Toe Pulse Volume (cc./10 cc. part)			Cardiac Output (cc./min)			Stroke Volume (cc.)			Pulse Rate		
Control	30 min.	60 min.	Control	30 min.	60 min.	Control	30 min.	60 min.	Control	30 min.	60 min.	Control	30 min.	60 min.	Control	30 min.	60 min.
0.63	0.24	0.21	.0054	.0020	.0025	.0007	.0026	.0018	7040	6213	6090	83.7	75.7	78.0	83	82	78
2.17	1.25	0.22	.0140	.0086	.0033	.0003	.0017	.0002	4627	4911	4603	60.8	72.1	65.7	76	68	70
0.15	0.10	0.12	.0018	.0010	.0013	.0003	.0030	.0012	6308	6353	5833	76.0	77.4	71.1	83	82	82
—	—	—	.0030	.0017	.0010	.0010	.0120	.0160	4596	3738	3524	68.0	50.4	55.0	67	74	64
2.16	1.62	1.44	.0083	.0060	.0055	.0066	.0068	.0066	5773	4465	3679	77.0	81.0	70.0	75	55	52
1.28	0.80	0.50	.0065	.0039	.0025	.0018	.0052	.0052	5669	5136	4746	73.1	71.3	68.0	77	72	69
—	−37.5	−60.9	—	−40	−61.5	—	+188	+188	—	−9.4	−16.2	—	−2.4	−7.0	—	−6.5	−10.4

Oxygen Consumption (cc./min).			Arterial Oxygen Capacity (vol. %)			Brachial Arterial Oxygen Content (vol. %)			Pulmonary Arterial Oxygen Content (vol. %)			Arteriovenous Oxygen Difference (vol. %)			Arterial Oxygen Saturation (%)		
Control	30 min.	60 min.	Control	30 min.	60 min.	Control	30 min.	60 min.	Control	30 min.	60 min.	Control	30 min.	60 min.	Control	30 min.	60 min.
211	215	215	16.50	16.68	16.68	14.83	15.25	15.25	11.83	11.79	11.72	3.00	3.46	3.53	89.8	90.8	90.8
206	194	203	13.72	13.15	13.35	12.40	11.79	12.07	7.97	7.84	7.66	4.43	3.95	4.41	90.3	89.6	90.4
229	223	224	13.00	12.85	13.00	11.85	11.75	11.81	8.21	8.24	7.97	3.63	3.51	3.84	91.0	91.4	90.8
189	169	160	16.35	16.70	16.75	15.07	15.56	15.09	10.96	11.05	10.55	4.11	4.52	4.54	91.5	93.1	90.0
224	192	188	12.91	12.54	12.50	11.14	10.24	10.43	7.26	5.94	5.32	3.88	4.30	5.11	86.2	81.0	83.4
212	199	198	14.50	14.38	14.45	13.06	12.92	12.93	9.25	8.97	8.64	3.81	3.95	4.29	89.9	89.2	89.1
—	− 6.1	−6.6	—	−0.8	−0.3	—	−1.0	−0.9	—	−3.0	−6.6	—	+3.5	+11.2	—	−0.7	−0.9

Pressures are recorded as systolic, diastolic and mean pressures. Average pressures are mean pressures.

4. Right Auricular Pressure. The pressure in the right auricle fell in every instance in both groups of patients. The reduction of the right auricular mean pressure from the average resting level was 36.3 per cent in the low, and 53.1 per cent in the high spinal group. It could be presumed that had it been feasible to record right auricular pressures in the latter group at the 30 minute period, even lower levels might have been found. The basal right auricular mean pressures were within the normal range in all except one patient (N. W.) in whom it was 19.0 mm. of Hg.

5. Pulmonary Arterial Pressure. The pulmonary arterial pressure decreased in all subjects. The maximal reduction from the average mean resting level was 17.4 per cent in the low, and 34.2 per cent in the high spinal group. While decreases of as much as 5 mm. of Hg may be demonstrable in the pulmonary arterial pressure of resting patients when serial pressures are recorded, the uniform reductions recorded in all subjects and the 100 per cent difference between the low and high spinal groups lend significance to the values.

It will be noted that the central and peripheral blood pressures and the cardiac index undergo essentially similar reductions with the induction of spinal anesthesia (fig. 1).

6. Oxygen Consumption. This showed a reduction in 8 of 10 patients, with no change in one (L. S.) and a definite rise in another (F. D.) patient. Slightly greater reductions occurred in the high spinal group than in the low spinal group.

7. Brachial Arterial Oxygen Content. The oxygen content of brachial arterial blood fell slightly in all patients with the exception of patients L. S. and M. G., in whom slight increases were noted. The average changes were from 13.06 to 12.92 in the low, and from 13.14 to 12.54 volumes per cent in the high spinal group. These slight changes are accounted for solely by the slight but constant reduction in the arterial oxygen capacity (see below).

8. Pulmonary Arterial Oxygen Content. This was ultimately reduced in all patients studied. The average decrease in the low spinal group was from 9.25 to 8.64, and in the high spinal group from 9.23 to 7.49 volumes per cent.

9. Arteriovenous Oxygen Difference. In the low spinal group a rise from the average basal level of 3.81 to 4.29 volumes per cent was noted, whereas in the high spinal group there was an average increase from 3.91 to 5.05 volumes per cent.

10. Brachial Arterial Oxygen Capacity. In the low spinal group this changed inconstantly and insignificantly, but in subjects to whom high spinal anesthesia was given there was a definite trend toward a decrease in capacity.

11. Arterial Oxygen Saturation. No significant alteration was noted in any subject with the exception of patient T. D., in whom there was a decrease from 86.2 to 81.0 and 83.4 per cent at the 30 and 60 minute periods respectively. This patient was 75 years of age and had significant pulmonary disease. Anesthesia to the level of T-4 to T-5, superimposing a decreased ventilation upon a probably reduced alveolar-pulmonary capillary oxygen diffusion, most likely accounted for the reduction which was observed.

12. Hematocrit Level. Although the individual values are not tabulated, there was an average decrease of 1 per cent in the low, and 2 per cent in the high spinal group. Constant decreases occurred in all instances, equal in specimens withdrawn simultaneously from the brachial and pulmonary arteries.

In both low and high spinal anesthesia, the reduction in brachial arterial oxygen capacity, hematocrit level and brachial arterial oxygen content can be explained partly by hemodilution from the catheter drip system and the withdrawal of numerous blood specimens. There is some evidence, however, that spinal anesthesia per se may produce such reductions, possibly by the displacement of red cells in the capillary bed.[39] The causes of these changes were not assessed.

13. Peripheral Blood Flows and Pulse Volumes. These underwent divergent responses in the fingers and toes in the low spinal group In the finger the blood flow was reduced from 1.28 to 0.5 cc. per 10 cc. of part per minute, and the pulse volume fell from 0.0065 cc. to 0.0025 cc. per 10 cc. of part. On the other hand

Pressures are recorded as systolic, diastolic and mean pressures. Average pressures are mean pressures.

TABLE 2.—*The Hemodynamic and Blood Oxygen Changes Induced by High Spinal Anesthesia*

Patient	Age	Sex	Diagnosis	Anesthetic & Level mg.	Brachial Arterial Pressure (mm. of Hg)			Right Auricular Pressure (mm. of Hg)		Pulmonary Arterial Pressure (mm. of Hg)		
					Control	30 min.	60 min.	Control	60 min.	Control	30 min.	60 min.
J. K.	56	M	Senility	Procaine 150	132/78	84/58	102/60	6.1/3.0	5.9/2.0	28.7/9.5	22.0/8.5	25.0/10
				T-3	102.0	73.0	80.4	4.9	4.32	18.7	16.7	17.5
F. B.	43	F	Obesity	Procaine 175	138/83	—	68/37.5	8.0/−2.5	2.0/−1.0	21.5/11	—	16.5/7.7
				T-2	105.0	—	52.0	4.4	0.4	16.8	—	11.1
M. G.	41	F	Abdominal mass	Procaine 150	113/69	67/45	87/60	3.0/1.5	−2.5/−2.0	16.5/6.5	9.5/2.5	10.0/2.5
				T-1	93.0	55.8	73.2	2.1	−1.2	11.5	6.3	6.3
F. D.	46	F	Paroxysmal hypertension	Procaine 150	114/66	54/36	66.42	5.2/2.4	4.2/1.6	15.5/8.5	10.1/5.5	11.5/6.8
				T-1 and 2	91.0	43.8	53.8	3.47	3.1	12.5	7.9	8.4
T. G.	60	M	Drug reaction	Procaine 175	145/71	63/36	75/41	10.5/1.8	4.7/1.2	17.5/9.7	12.5/4.7	13.5/6.0
				T-1 and 2	101.4	47.9	56.7	4.8	2.6	14.8	8.4	10.2
Averages.....	49.2				98.5	55.1	63.2	3.93	1.84	14.9	9.8	10.7
Percentile change.....					—	−44.0	−35.8	—	−53.1	—	−34.2	−28.2

Finger Blood Flow (cc./10 cc. part/min.)			Finger Pulse Volume (cc./10 cc. part)			Toe Pulse Volume (cc./10 cc. part)			Cardiac Output (cc./min.)			Stroke Volume (cc.)			Pulse Rate		
Control	30 min.	60 min.	Control	30 min.	60 min.	Control	30 min.	60 min.	Control	30 min.	60 min.	Control	30 min.	60 min.	Control	30 min.	60 min.
0.29	1.36	0.73	.0021	.0105	.0070	.0016	.0060	.0064	5204	3876	4365	64.2	50.2	55.2	81	77	79
0.32	—	1.88	.0020	—	.0250	.0013	—	.0081	5718	—	3060	68.6	—	54.6	83	—	56
—	—	—	—	—	—	—	—	—	3427	2360	2707	39.3	27.4	32.6	87	86	83
0.28	0.84	1.10	.0016	.0140	.0065	.0010	.0095	.0110	3873	3438	4230	47.2	45.2	52.2	82	76	81
0.39	0.61	0.73	.0025	.0097	.0118	.0035	.0075	.0075	5315	3315	4449	66.0	51.0	74.0	80	65	60
0.32	0.94	1.11	.0021	.0114	.0126	.0018	.0077	.0082	4707	3247	3762	57.0	43.5	53.7	82.6	76.0	71.8
—	+193	+247	—	+443	+500	—	+327	+366	—	−31.0	−20.0	—	−23.7	−5.7	—	−8.0	−13.1

Oxygen Consumption (cc./min.)			Arterial Oxygen Capacity (vol. %)			Brachial Arterial Oxygen Content (vol. %)			Pulmonary Arterial Oxygen Content (vol. %)			Arteriovenous Oxygen Difference (vol. %)			Arterial Oxygen Saturation (%)		
Control	30 min.	60 min.	Control	30 min.	60 min.	Control	30 min.	60 min.	Control	30 min.	60 min.	Control	30 min.	60 min.	Control	30 min.	60 min.
218	195	203	13.78	13.15	12.75	12.36	11.58	11.35	8.21	6.55	6.70	4.15	5.03	4.65	89.6	88.0	89.0
195	—	172	15.85	—	15.80	14.38	—	14.28	10.97	—	8.65	3.41	—	5.62	90.7	—	90.3
134	122	127	15.63	15.63	15.48	14.30	14.65	14.35	10.38	9.46	9.66	3.91	5.19	4.69	94.1	93.7	92.7
153	155	176	15.09	15.09	15.09	13.80	13.68	13.73	9.85	9.26	9.50	3.95	4.42	4.16	91.4	90.6	90.9
219	184	198	11.80	11.41	11.41	10.84	10.26	10.30	6.72	4.71	5.85	4.12	5.55	4.45	91.8	90.0	90.2
184	164	175	14.43	13.82	14.11	13.14	12.54	12.80	9.23	7.49	8.09	3.91	5.05	4.71	91.5	90.5	90.6
—	−10.8	−4.9	—	−4.2	−2.2	—	−4.5	−2.6	—	−18.8	−12.3	—	+22.6	+17.0	—	−1.0	−1.0

Pressures are recorded as systolic, diastolic and mean pressures. Average pressures are mean pressures.

the pulse volume in the toe rose from a basal average of 0.0018 to 0.0052 cc. per 10 cc. of part. These divergent responses between fingers and toes were a constant feature in all the studies with low spinal anesthesia. The vasoconstriction in the finger persisted and in most instances progressed for the duration of the investigation.

On the other hand the induction of high spinal anesthesia was followed by increased rates of circulation in both the fingers and toes. In this group the finger blood flow rose from a resting average level of 0.32 cc. to 1.11 cc. per 10 cc. of part per minute, and the finger pulse volume from an average of 0.0021 cc. to 0.0126 cc. per 10 cc. of part; the pulse volume in the toe increased from 0.0018 cc. to 0.0082 cc. per 10 cc. of part. The circulatory responses in the fingers are in contrast to those developing after low spinal anesthesia, and are the result of vasomotor paralysis of the preganglionic sympathetic outflow to the upper extremities in high spinal anesthesia. In this group the peripheral circulation tended to increase further in most cases at the 60 minute period when the blood pressure was rising.

14. Estimated Total Peripheral Resistance (T.P.R.). Total peripheral resistance showed a maximal reduction of 13.5 per cent in the low, and 18.8 per cent in the high spinal group. This fell to a greater extent in those patients who showed the greater decreases in blood pressure, but the validity of the formula is open to question when treating arteriovenous pressure differences of less than 80 mm. of Hg.[15]

15. Calculated Left Ventricular Work (L.V.W.). This decreased in both groups. The low spinal group showed an average maximal reduction of 30 per cent from the basal level, and the high spinal group a maximal reduction of 62.4 per cent. The one patient (G. T.) (low spinal), who showed an increase in left ventricular work, failed to develop the usual decrease in blood pressure, and the cardiac out-

TABLE 3.—*The Changes in Cardiac Index, Left Ventricular Work and Estimated Total Peripheral Resistance Induced by Low and High Spinal Anesthesia*

Low Spinal Anesthesia

Patient	Cardiac Index (L./min.)			Left Ventricular Work (Kg. meters/min.)			Total Peripheral Resistance (Absolute units)		
	Control	30 min.	60 min.	Control	30 min.	60 min.	Control	30 min.	60 min.
L. S.	4.24	3.70	3.64	8.27	5.82	5.51	16.5	14.9	14.7
N. W.	3.23	3.43	3.21	6.12	5.73	6.20	28.2	23.4	28.9
G. T.	3.68	3.71	3.41	7.93	8.33	8.02	19.5	20.2	23.0
P. P.	2.43	1.97	1.87	6.64	3.88	3.80	31.0	27.5	30.3
T. D.	3.30	2.50	2.07	9.04	3.97	3.14	26.8	19.6	22.9
Averages	3.37	3.06	2.84	7.60	5.55	5.33	24.4	21.1	24.0
Percentile change	—	−9.2	−15.7	—	−27.0	−30.0	—	−13.5	−1.6

High Spinal Anesthesia

Patient	Cardiac Index (L./min.)			Left Ventricular Work (Kg. meters/min.)			Total Peripheral Resistance (Absolute units)		
	Control	30 min.	60 min.	Control	30 min.	60 min.	Control	30 min.	60 min.
J. K.	2.79	2.08	2.34	7.17	3.80	4.73	26.2	25.1	24.4
F. B.	3.00	—	1.62	8.10	—	2.14	24.5	—	22.7
M. G.	2.46	1.69	1.94	4.30	1.78	2.67	36.2	31.6	36.1
F. D.	2.76	2.45	3.02	5.73	2.08	3.02	31.3	17.0	16.7
T. G.	2.90	1.80	2.43	7.28	2.14	3.40	25.4	19.3	17.0
Averages	2.78	2.00	2.27	6.52	2.45	3.20	28.7	23.3	23.4
Percentile change	—	−28.1	−18.4	—	−62.4	−50.9	—	−18.8	−18.7

Pressures are recorded as systolic, diastolic and mean pressures. Average pressures are mean pressures.

put was maintained. It is interesting that this one patient was exceptional in that the level of anesthesia was as low as T-11 and the blood pressure rose slightly.

16. Clinical Observations. The clinical events which accompany low spinal anesthesia are well known, but those which occur during high spinal anesthesia are of some interest. The authors have employed the procedure in 25 conscious patients, 20 of whom will be discussed in other reports concerned with studies in blood flow in surgical patients[27] and in individual organs.[26] As the anesthetic agent rises in the subarachnoid space, and particularly when levels above the fourth thoracic dermatome are rendered analgesic, the patients often yawn repeatedly. Following this event there may be a period of transient and slight nausea which usually subsides quickly and spontaneously or is alleviated by the inhalation of 100 per cent oxygen for a few minutes. In two instances severe nausea and vomiting occurred. This was the case in patient F. B. in whom it was not possible to record values at the 30 minute period since she was maintained on 100 per cent oxygen until that time because of nausea and retching associated with almost total body analgesia. Hyperventilation and considerable apprehension on the part of the patient may occur. In one instance the patient became so emotionally upset that it was thought best to terminate the procedure. In a third subject a 15 minute period of Cheyne-Stokes respiration occurred.

Although it has been implied that these occurrences, and particularly vomiting, are related to the high level of the anesthesia,[32] our impression is that they are more likely associated with the rapidity with which the anesthetic agent rises in the subarachnoid space. Individual variations in the response to spinal anesthesia also play a role. In both instances mentioned, the patients became anesthetic to the clavicles in approximately two or three minutes. On the other hand, three patients (M. D., F. D., and T. G.) who developed sensory anesthesia to the first thoracic level within an optimum period of 8 to 10 minutes, experienced no untoward reactions. When profound hypotension develops, however, nausea, vomiting and other symptoms become apparent regardless of the rapidity with which anesthesia is induced.

As has been noted by others,[9, 16] the peripheral arterial pressure usually reaches a maximal reduction within 15 minutes. This is maintained for about an hour, and then a gradual rise commences. The blood pressure returns to near basal levels within two or two and one-half hours, and this can be accelerated by the parenteral administration of a vasopressor agent such as Neosynephrine, which is free to act directly on the decentralized blood vessels. The administration of such an agent is seldom indicated.

Discussion

The hemodynamic changes produced by low and high spinal anesthesia are similar, with the exception of the effects on the peripheral circulation.

1. Blood Pressure. When vasoconstrictor drugs are not used, a constant accompaniment of both low and high spinal anesthesia is a reduction of the blood pressure. If the anesthetic agent is confined to the lower thoracic segments, the reduction in blood pressure is usually slight. If the anesthetic agent is allowed to reach the upper thoracic segments, marked lowering of the blood pressure usually occurs.

The cause of the hypotension in spinal anesthesia is not settled. Hematogenous intoxication,[23] direct action on the medullary centers[8, 33, 35] and reduced secretion of adrenaline by paralysis of the adrenal nerves[34] are hypotheses which may be mentioned as of historical interest. The hypothesis that paralysis of the skeletal muscles with resultant loss of tone[14, 18] leads to a diminished venous return to the heart has been found invalid.[1, 2, 38] The role of respiratory depression, although of little importance in low spinal anesthesia, merits consideration as a cause of hypotension in high spinal anesthesia. The view that paralysis of the sympathetic vasconstrictor fibers to the arterioles, capillaries and veins occurs at the preganglionic level is the one best explaining the hemodynamic changes occurring in spinal anesthesia, whether high or low.

The argument that systemic hypotension is due primarily to respiratory depression or paralysis may now be examined. In high spinal anesthesia complete intercostal depression or even paralysis usually develops, and the respiratory pattern becomes diaphragmatic. There is no doubt that paralysis of the abdominal and thoracic muscles interfers with respiratory function,[14, 21] causing a reduction in the vital capacity,[21] but that this so impairs the venous return to the heart as to explain the hypotension has been questioned.[7, 23, 38, 39] Our observations suggest that respiratory depression is not the cause of the systemic hypotension which develops during high spinal anesthesia, since this occurs even when respiratory function is maintained efficiently by intermittent positive pressure breathing.[26] One recent investigation[38] has shown rather conclusively by the use of differential spinal block, that extreme hypotension can exist with little or no intercostal paralysis. Should paralysis of the phrenic nerves occur with high spinal anesthesia, cerebral anoxia and secondary vasomotor collapse would result, were artificial respiration not initiated. The fact that extreme hypotension can exist in the absence of phrenic or intercostal nerve paralysis,[38] and that such hypotension cannot be corrected by means of artificial respiration, supports the view that respiratory paralysis is not a major factor in the hypotension. Our observations indicate that respiratory exchange is sufficient to saturate pulmonary blood, since the oxygen saturation of the arterial blood remained virtually unaltered even in the face of marked degrees of hypotension. Contrariwise, spinal anesthesia may be attended by a significant and dangerous decrease in arterial oxygen saturation in the patient with impaired respiratory function, as occurred in one patient (T. D.). This does not occur if efficient aided or artificial respiration is maintained.[26]

Experimental and clinical evidence has accumulated supporting the role of sympathetic vasoconstrictor paralysis in the production of the hypotension during spinal anesthesia. It is manifestly impractical to consider arteriolar paralysis and paralysis of the postarteriolar beds separately,[29, 32, 43] as it is extremely unlikely that spinal anesthesia could effect one and not the other. The demonstration that serial destruction of the spinal cord in dogs[19, 36] produces profound hypotension only when the fourth thoracic segment is destroyed suggests that up to a certain level the body can compensate for the loss of sympathetic vasoconstrictor elements and maintain a fairly normal blood pressure. These findings have been substantiated by spinal procaine block in dogs[4, 10, 42] in which the blood pressure is well maintained as long as the upper thoracic segments are not paralyzed. The results of this study would support this contention, since the fall in blood pressure in the low spinal group was not usually severe. The demonstration that spinal anesthesia produces no appreciable drop in blood pressure after total sympathectomy[5] is additional proof of the role of that system in the production of the hypotension of spinal anesthesia.

It is therefore suggested that the hypotension so constant in spinal anesthesia is the result of paralysis of vasomotor tone, proportional to the degree of sympathetic paralysis. The result is a decreased peripheral resistance and an increased capacity of the arteriolar and postarteriolar vascular beds in the anesthetized regions, factors which cause a reduction in the blood pressure. If vasomotor paralysis were the only factor, it should be possible to demonstrate an increased blood flow in all the anesthetized regions due to the release of arteriolar tone; there should be a decreased arteriovenous oxygen difference in the blood from those areas; and there should be an increase in the venous and right heart pressures secondary to the increased venous return. Our data do not support wholly these suppositions, but, in the light of data obtained during the course of observations on individual organ flows,[17, 30] indicate regional variations in the rate of blood flow and oxygen extraction.

2. Peripheral Blood Flow. The data in this report substantiate the observations of others,[6, 11, 29, 31, 38, 40] that the rate of blood flow increases in the extremities after spinal block, and that in the case of low spinal

anesthesia there is a compensatory vasoconstriction in the upper extremities. The increased blood flow in the anesthetized fingers and toes is maintained only so long as the mean blood pressure remains above the normal arteriolar pressure. When the mean arterial blood pressure falls below circa 30 mm. of Hg, the peripheral blood flow falls below the normal resting level.[26] In most cases of high spinal anesthesia such low levels of blood pressure do not occur.

3. Oxygen Consumption. This was found to be reduced by both low and high spinal anesthesia. This reduction was minimal in the subjects who had low spinal anesthesia and somewhat greater in the subjects who had high spinal anesthesia. Were one to consider only the average group changes, it would be difficult to ascribe significance to the reductions encountered which were maximally no greater than 10 per cent. However, a reduction was noted in four of five patients in each group, and the greater average reduction occurred in subjects who were given high spinal anesthesia. Hypotensive states in themselves may be associated with a drop in the basal metabolic rate.[3] An additional factor in spinal anesthesia is the existence of a flaccid paralysis of the striated muscles in the anesthetized areas, and a reduction of the oxygen utilization would be expected, proportional to the mass of paralyzed muscle.

4. Arteriovenous Oxygen Difference. In most cases of low and in all cases of high spinal anesthesia the arteriovenous oxygen difference is increased. If one were to assume that the increased blood flows noted in the fingers and toes are representative of similar changes occurring elsewhere in the entire vascular bed, it would be difficult to reconcile such increases with a rise in the arteriovenous oxygen difference and a fall in the cardiac output. The greatly increased arteriovenous oxygen differences noted particularly in high spinal anesthesia, are believed to be due to a combination of two factors: (a) a marked slowing of the rate of blood flow in areas other than the extremities, and, (b) the possible opening of prevenous channels that are normally nonfunctioning in the basal state. Investigations now in progress in this laboratory indicate that there is a definite reduction in the hepatic[30] and coronary[17] flows, with a greatly exaggerated relative extraction of oxygen from the splanchnic blood,[30] and a decreased extraction from the blood in the extremities. Kety and his associates[22] have shown that under differential spinal block in hypertensive patients, the hypotension so produced is associated with a reduction in the rate of cerebral blood flow.

Data have been reported[7, 39, 41] suggesting that a state of stagnation of the peripheral circulation exists in the anesthetized regions. That the circulation time increases has also been demonstrated.[13] It would follow from such observations that the arterial-venous oxygen differences in the blood from the involved areas would increase. The data presented in this report demonstrate an increased arteriovenous oxygen difference between the brachial and pulmonary arterial bloods, but this is attributed in part not to stagnation in the extremities, but rather to a decrease in the rate of flow and a predominant increase in the oxygen extraction in the splanchnic bed.[30]

5. Total Peripheral Resistance. This falls, provided there is a decrease in the blood pressure. Total peripheral resistance, however, does not afford a measure of regional variations in resistance. Increases in resistance in the renal[2] and splanchnic[30] vasculature have been demonstrated following the administration of spinal anesthesia, but they are slight, and the evidence ascribing such changes to selective vasoconstriction is lacking of conclusive proof.

6. Right Heart Pressures. Our data show a decrease in the pressures within the right auricle and the pulmonary artery, as has been found by others.[37] It has been shown that the peripheral venous pressures fall with the arterial pressure during spinal anesthesia.[1] That the drop in right heart pressures may be due to the release of vasomotor tone in the pulmonary arterioles is worthy of consideration, but it is probably not a factor of major importance. The reductions in right heart pressures noted herein are consistent with the finding of a decreased cardiac output, and with the view that there is an over-all reduction in the rate of blood flow in the viscera. The

evidence for this is the increased difference between the oxygen content of the brachial and pulmonary arterial bloods, associated with a decreased blood flow through the splanchnic,[30] coronary[17] and renal[2] beds, proportionately greater than the increased flow in the extremities.

7. Bradycardia. In general the heart rate slows after spinal anesthesia has become established. The bradycardia under high spinal anesthesia may be due to paralysis of the cardiac accelerator fibers. This explanation would not apply to low spinal anesthesia where the innervation of the heart is intact, and the heart rate similarly slows. In these cases it is difficult to explain the failure of the hydrostatic carotid sinus reflex to induce tachycardia. All the patients had a decrease in right heart pressure, due to a decrease in venous return to the heart. The tendency of this to cause bradycardia (Bainbridge reflex), may have overcome any activity on the part of the carotid sinus.

8. Cardiac Output. The cardiac output dropped in all patients after spinal anesthesia became established. In one patient the drop was minimal (F. D.) despite the fact that there was a profound drop in the blood pressure, and at the end of 60 minutes there was an actual increase in the output, a sequence of events which remains unexplained; in another (G. T.) the cardiac output did not change significantly, but neither did the blood pressure with an anesthetic level of only T-11. From the data already discussed it would appear that the decrease in the cardiac output is the result of a decreased venous return to the heart, and in general this decrease is greater after high than after low spinal anesthesia. A similar relationship exists between the right heart pressures under the two types of anesthesia.

9. Left Ventricular Work. With the exception of one subject (G. T.) who did not have a reduction of blood pressure following spinal anesthesia, all patients showed a significant decrease in left ventricular work. The greater reductions were observed in the patients who were given high spinal anesthesia, mainly a reflection of the diminished arterial pressure. Unpublished observations[17] reveal a marked decrease in coronary flow, with a stable or slightly reduced oxygen extraction. Under the circumstances it is possible that the reduced coronary circulation is sufficient to meet the lessened work demand of the myocardium.

It is believed that the cause of the cardiovascular changes observed in spinal anesthesia is the paralysis of the preganglionic sympathetic nerve fibers of the spinal cord, and these changes become more marked as higher cord levels are blocked. The vasomotor paralysis which follows leads to local alterations in hemodynamics. Although in the skin there is a demonstrable increase in the rate of blood flow in the anesthetized regions, it is possible that this increase may represent a combination of decreased resistance in the arteriolar bed and the opening of channels (metarterioles) not functioning in the basal state. It is reasonable to assume that there is an increased rate of blood flow in the muscles as has been found to occur in general anesthesia.[27] Our data show that there is a decreased venous return to the heart with an increased circulation in the extremities. This must result from a substantially greater reduction of venous return with increased oxygen extraction from other parts of the body, presumably, in the main, the splanchnic bed. This view is supported by the known decrease in renal flow[2] and by unpublished observations demonstrating a decrease in splanchnic and coronary blood flows. The increase in the arteriovenous oxygen difference is in itself indicative only of a greater relative extraction of oxygen by the body tissues, whether this be due to more prolonged contact between the tissues and the red cells (reduced rate of blood flow as in stagnant anoxia), to a greater surface contact (as a result of the opening of previously nonfunctioning vascular compartments), or both.

We have observed no significant ill effects in this group of patients consequent to the administration of high spinal anesthesia, provided that adequate oxygenation of the arterial blood is maintained. In no instance have pathologic reflexes appeared, and there has been no evidence of delayed neurologic derangement, nor of unusual depression of

kidney function as demonstrated by urinary concentration tests. No electrocardiographic changes indicative of myocardial anoxia have been demonstrated during or after the administration of anesthesia.

Summary and Conclusions

1. The hemodynamic changes induced by spinal anesthesia, low and high, were studied in 10 patients, without the use of vasoconstrictor drugs.

2. Certain effects upon hemodynamics were induced by both low and high spinal anesthesia, as follows:

(a) The cardiac output, the cardiac index and the stroke volume of the heart decreased. (b) The right auricular, the pulmonary arterial and the brachial arterial blood pressures fell. (c) The total peripheral resistance decreased. (d) The heart rate decreased in four out of five patients who had low, and in all subjects who had high spinal anesthesia. This is the usual occurrence following initial stabilization, provided physical and psychic stimuli are not present. (e) The rate of oxygen consumption decreased. (f) The calculated work of the left ventricle decreased in all except one case in whom the systemic blood pressure did not fall. (g) The pulmonary arterial oxygen content dropped, and, with relatively little decrease in the brachial arterial oxygen content and no decrease in arterial oxygen saturation, the arteriovenous oxygen difference increased.

3. The effects upon the blood flow in the extremities differed between low and high spinal anesthesia, as follows:

(a) The peripheral blood flow under low spinal anesthesia increased in the toes, but diminished in the fingers. (b) The peripheral blood flow and pulse volume increased in both fingers and toes under high spinal anesthesia.

4. The differences in the hemodynamic effects of low and high spinal anesthesia are only quantitative, and are more marked with high spinal anesthesia.

5. The hemodynamic changes induced by spinal anesthesia are attributed to vasomotor paralysis.

6. Acute sequential studies of the circulation, which may shed light on the immediate adjustments of the circulation to spinal anesthesia, are needed.

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The Determination of Cardiac Output by a Continuous Recording System Utilizing Iodinated (I^{131}) Human Serum Albumin

II. Clinical Studies

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A method previously described for the determination of cardiac output by the injection of iodinated (I^{131}) human serum albumin has been extended to a study of its application to patients. A technic suitable for clinical use has been described and values obtained have been compared with those simultaneously determined by cardiac catheterization. The average deviation from Fick principle values was ±8.3 per cent over a range from −8.4 per cent to +18.7 per cent. Certain precautions in technic necessary for accuracy have been stressed.

IN AN ATTEMPT to develop a convenient, accurate method for cardiac output determination which can be used at fairly frequent intervals over periods of days, weeks, or months, rather than during a few hours, the blood dilution principle of Stewart[1] and Hamilton[2] has been adapted for the use of tracer doses of I^{131} attached to human serum albumin. The radioactivity of the arterial blood concentration has been measured by a scintillation counter as blood is flowing over the counter and the dilution curve continuously recorded by a Berkeley counting rate computer, used in conjunction with a scaler and Esterline Angus graphic meter.

The experimental details of the necessary instrumentation and technic were studied first in dogs, and previously reported.[3] It was found that the cardiac output determined by this method showed an over-all agreement of +9 per cent with values simultaneously determined by an optically recording aortic flow meter if allowance was made for the unmeasured coronary flow in the rotameter values. For details of the recording apparatus and calculations involved in this method, the previous work should be consulted.

The purpose of this paper is to describe the use of this modification of the dilution principle in humans and to compare the results with the values derived from simultaneously determined Fick outputs, using the cardiac catheterization technic. In previous animal work, the dilution and rotameter outputs were determined simultaneously for identical temporal periods. In using the Fick principle in humans, exact simultaneity was not possible, since determination of oxygen consumption required usually 4 to 6 minute periods, whereas dilution curves were usually inscribed within a 20 to 50 second period. Although a handicap, it is thought that inherent differences in the use of the methods have not detracted seriously from the data obtained.

Technic

The general procedure of technic followed in these studies was similar to that previously reported.[3] Figure 1 represents a block diagram schema of the technic. Into either brachial or femoral artery was inserted a Cournand No. 18 arterial needle after infiltration with 2 per cent procaine. This has usually been a perfectly painless procedure, if care is taken to infiltrate sufficiently around the artery. The needle was so adjusted within the arterial lumen that a free, pulsatile flow existed when the stylette

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was removed. This was a necessary precaution, and unless this free, pulsatile flow could be maintained, the needle was removed and reinserted.

A stainless steel tube of 2 mm. bore, curved to fit closely over the counter crystal, was used to lead blood past the counter. The inner surface was silicoined to aid in clot prevention. Rubber tubing was attached to both ends of the steel tubing, for leading blood from the needle, and for collecting blood in a beaker after it had passed the counter (fig. 2). This steel tube and counter were completely shielded by lead bricks 1½ inches thick and placed in a suitable unit to insure stability when used. Prior to each determination, a small amount of saline containing heparin was flushed through this external flow system. To record the curve of dilution, it was necessary merely to connect this system to the arterial needle, and when blood was dripping freely into the beaker, the calculated volume of tagged albumni was rapidly delivered into the circulation. As soon as definite recirculation was identified on the tracing, the flow was stopped, and the system disconnected from the arterial needle and flushed with tap water until clear. This flushing procedure has been found to eliminate completely any radioactive residue. After a 10-minute interval, the system was reconnected to the arterial needle, and blood allowed to drip slowly into test tubes for measurement of the final concentration of radioactivity in the blood for determination of the blood volume. The final dilution of the radioactivity in the blood was taken simultaneously as it passes through the flow system in order that the system may be calibrated in terms of the blood volume. The mean dilution during the period for the primary circulation as related to the final dilution indicates what portion of the total blood volume flowed during this time. The measurement of the total blood volume therefore permits calculation of the cardiac output in terms of volume per period of time (liters per minute). The complete analysis is given in detail in the previous publication which shows that the cardiac output by the dilution method may be expressed by the equivalent expression:

$$F = \frac{\frac{C_f}{C_{av}} V}{T}$$

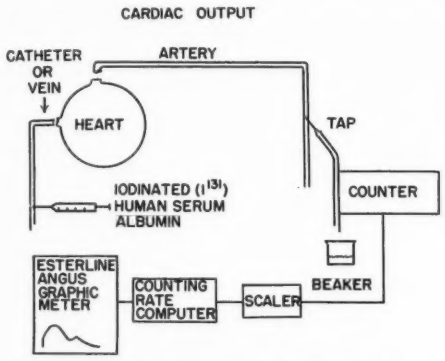

FIG. 1. Schematic diagram of experimental set-up for determination of cardiac output.

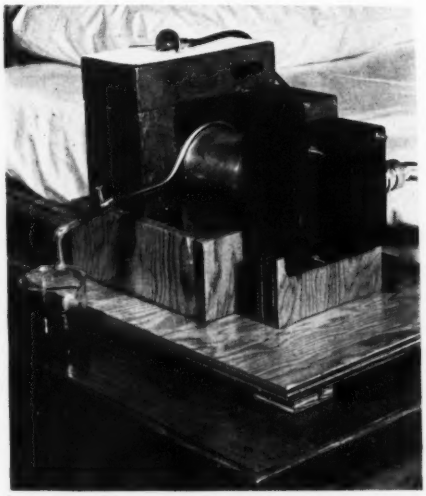

FIG. 2. View of partially shielded detector head (scintillation counter) and tubing for tapping arterial flow. In actual use complete shielding of the stainless steel tube and counter is required.

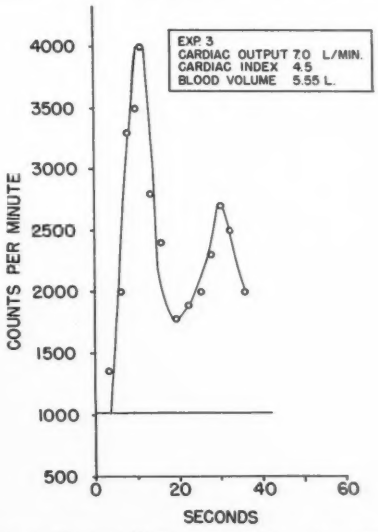

FIG. 3. Typical dilution curve. Experiment 3. Base line refers to background level.

where F is the cardiac output in terms of volume per unit time, C_f is the final concentration, C_{av} is the average concentration, V is the blood volume and T is the period of first circulation flow. Typical output curves are shown in figures 3 and 4. It can be seen that the primary dilution curve in figure 3 is tall and narrow as contrasted with figure 4. Calculations show that the cardiac output in figure 3 is 28 per cent greater, whereas blood volume is 9 per cent less than in figure 4.

Injection of the tagged albumin was made either through the catheter or into an arm vein through a No. 18 gauge needle. If given through the catheter, the injection was immediately followed by rapid flushing with 15 to 20 cc. of normal saline. Flushing of the needle in the peripheral vein was also carried out on these patients. In subsequent studies, it was found, however, that flushing is not necessary if the volume of isotope is kept reasonably large (3 to 4 cc.). Arm positioning is of importance in that there must be rapid delivery of the material into the right heart. Significant obstruction to free flow may result from incomplete relaxation of the upper arm and shoulder girdle and excessive abduction or outward rotation.

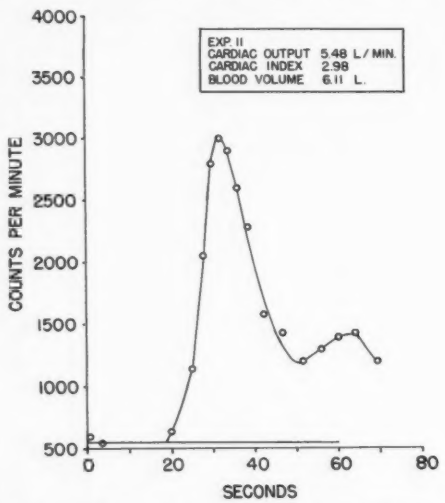

FIG. 4. Typical dilution curve. Experiment 11

For a period of 24 hours before and continuing for 24 to 72 hours following the study, Lugol's solution, 10 drops three times daily, was administered to minimize the uptake of the dissociated I^{131} by the thyroid gland.

PROCEDURE

Patients from the medical wards were studied in the morning before breakfast following an 8 to 10 hour night's rest. Sodium seconal, 0.1 Gm., was given approximately 45 minutes before cardiac catheterization was begun. Following the placing of the catheter in the right heart or pulmonary artery, the arterial needle was inserted into either the femoral or brachial vessel. After a rest period of 20 to 30 minutes, cardiac output was determined by both the Fick principle and dilution method as nearly simultaneously as possible: arterial and venous blood samples were drawn, the determination of oxygen consumption begun, and tagged albumin rapidly injected. Following the initial dilution curve, a second set of arterial and venous samples was usually drawn for oxygen analysis. If the Sanborn metabolator was used, oxygen consumption was started after the inscription of the curve. If two sets of blood samples were drawn, the A-V differences were usually averaged, unless the interval between samples was excessive, in which case the set drawn nearest to the recorded dilution curve was used. In one instance, an arterial needle was inserted into two arteries and arterial and mixed venous blood was drawn during the dilution determination. No apparent greater accuracy was obtained in this one study and because of the inconvenience, the sequential procedure was preferred.

Oxygen content of blood was determined either by Van Slyke analysis[4] or by the spectrophotometer method of Hickam,[5] or by both. Oxygen consumption was calculated from the slope of curve of the utilization in the Sanborn clinical metabolator in 10 patients and in two patients by collection of expired air in a Tissot apparatus with oxygen analysis performed by the Pauling gas analyzer.

RESULTS

Out of 15 attempts, there were 12 single satisfactory runs on 11 patients from the technical standpoint of both procedures. Three were unsatisfactory and will be discussed separately.

The table gives the data upon which the calculations were based, catheter position in the right heart, amount and route of iodinated albumin administered in addition to the blood volume, cardiac outputs and the percentile deviation of the dilution from the Fick output.

The range of deviation was from -8.4 per cent to $+18.7$ per cent with an average deviation of ± 8.3 per cent. These studies are in substantial agreement with previously reported studies using T-1824 dye as the diluted material.[6-8] Also to be noted is the large range of outputs exhibited by these patients, which vary from 2.83 liters per minute in run number 5 in a patient with moderately severe chronic congestive heart failure, to 11.45 liters per

minute in run number 10 on a patient recovering from acute alcoholism. Agreement in values was good over the range of outputs studied.

In comparing studies 4 and 5, which constitute two separate determinations 21 days apart on the same patient, the absolute decrease in output as shown by each was approximately the same, 0.75 liters per minute by the Fick and 0.57 liters per minute by the dilution technic, giving relative decreases of 20.9 per cent and 14.5 per cent respectively.

ployed can be used to calculate accurately the cardiac output.

The radioactivity of the injected iodinated (I^{131}) human serum albumin was kept to the minimum amount that was still sufficiently high to give reasonable counting rates. This was found to be in the range of 120 to 160 μc., giving a final dilution concentration of 0.02 to 0.03 μc. per cubic centimeter.*

TABLE 1.—*Summary of Data on Which Calculations Were Based in 12 Successful Studies*

Run	Pt.	Diagnosis	Art. O_2	Ven. O_2	A-V	O_2 Cons.	Cath. Pos.	Inj. Site	Dose μc	Blood Vol. Liters	Cardiac Output Fick	Cardiac Output Dilution	% Deviation of Dilution from Fick
1	F.P.	Alcoholism	18.3	14.6	3.7	255	R.V.	Cath.	159	5.18	6.90	6.57	−4.8
2	T.J.	Diabetes	19.0	15.5	3.5	280	P.A	Cath.	154	5.76	8.00	8.80	+10.0
3	H.T.	Cancer of lung	8.4	4.5	3.9	235	P.A.	Cath.	135	5.55	6.02	7.00	+17.0
4	N.L. A	Artscl. heart dis.	17.9	13.3	4.6	165	R.A.	Cath.	147	5.17	3.58	3.92	+9.5
5	N.L. B	Artscl. heart dis.	18.8	12.8	6.0	170	R.A.	Cath.	134	5.04	2.83	3.35	+18.7
6	W.C.	Arteritis	19.1	15.55	3.55	210	R.A	Cath.	143	4.84	5.92	5.95	+0.5
7	R.B.	Susp. axillary A-V fistula	17.3	13.4	4.0	270	R.A.	Cath.	159	4.33	6.75	6.27	−7.1
8	G.G.	Convalescent pneumonia	17.0	11.8	5.2	240	P.A.	Cath.	146	5.74	4.62	5.38	+16.5
9	F.M.	Acute alcoholism	16.8	13.5	3.3	378	R.A.	Periph. vein	145	6.57	11.45	11.30	−1.3
10	C.W.	Convalescent pneumonia	13.0	9.7	3.3	199	P.A.	Periph. vein	142	5.89	6.00	6.28	+4.6
11	L.G.	Syphilitic heart dis.	16.4	11.8	4.6	275	R.A.	Cath.	147	6.11	5.98	5.48	−8.4
12	I.J.	Emphysema	15.4	9.9	5.5	172	P.A.	Periph. vein	140	5.18	3.13	3.16	+1.0
Average													±8.3

COMMENT

Although the details of the technic, such as time of drawing bloods, placing of catheter tip, site, and type of injection of the iodinated protein varied somewhat, it appears that no consistently demonstrable errors were introduced, since, in general, satisfactory agreement of the dilution method with the Fick principle was obtained. Both methods are theoretically sound and this clinical study supports our previous conclusions from animal work, that the curves of blood dilution of tagged albumin recorded by the apparatus and technic em-

The advantage of the higher concentration is that it is possible to record a greater number of points of concentration per unit time. At the concentrations used, a point was recorded every one or two seconds. This is at a slower rate than previous determinations,[3] but was considered sufficiently adequate to describe the dilution curve. In addition to the dilution curve, the only other data required are the

* A modification has recently been made to incorporate a thallium-activated sodium iodide crystal rather than an anthracene crystal as the detector. The greater detection efficiency will then enable either a smaller dose to be given or a higher counting rate to be obtained and subsequently more points recorded on the curve.

final concentration for calibration of the flow and the blood volume.

Difficulties with obtaining these data have been minor, although precautions have been found necessary in the delivery of the dose. This dose has been given in volumes of from 2 to 5 cc., which offers a fair compromise between being small enough to effect delivery within a short period of time and large enough to make error in delivery relatively small. The syringe used was calibrated in terms of output for one stroke and this output insured by fitting a double stopcock to the syringe and following the injected radioactive albumin with a 15 to 20 cc. flushing of normal saline solution.

Although care is taken during this injection, occasionally all the radioactive material is not inserted into the vein, but lies subcutaneously at the site of injection. It has become routine to check for any radioactivity remaining in the arm by placing the detector over this area and comparing it with the counting rate over the arm not given the injection. After these steps had been taken, very little difficulty has been encountered with the blood volume determination. A spot check has been made by comparing a simultaneous determination with the "blue dye" method which showed a deviation of less than 6 per cent. Two separate determinations on one patient (runs 4 and 5) by this method have shown a deviation of less than 3 per cent.

Loss of radioactivity in the blood drained off during the initial recording of the curve may theoretically affect the final blood volume calculation, if the drained blood contains a large proportion of the injected dose. However, with the small blood loss (30 to 50 cc.), only a minor difference is possible. In run number 2 the average concentration of the blood drained off into the beaker was about 30 per cent higher than the final dilution. For 50 cc. of blood removed this loss of injected activity corresponds to an error in blood volume of 15 cc., or 0.3 per cent.

In three patients, agreement was poor. In one, the Fick output of 3.3 liters per minute was recorded as 2.08 liters per minute by the dilution method, but partial clotting had occurred in the arterial needle and free flow through the system never obtained. Previous controlled studies in animals[3] had shown that good arterial flow is necessary or falsely low output values will result from radioactivity diffusion within the stagnant segment of blood over the recording counter. In another, 2 cc. of tagged material was injected into the catheter without flushing. With the large catheter dead space, a smaller amount than used in the calculations was actually delivered, giving a falsely high value for the blood volume. In the third patient, the Fick output was 3.5 liters per minute as compared to a dilution output of 6.2 liters per minute. Technical difficulties with blood analysis and oxygen consumption gave reason to doubt the validity of the Fick output.

We have not attempted duplicate data or serial determinations in these patients, although this has been done in animals. At the time of this study, sufficient counter sensitivity had not been obtained to enable duplicate measurements to be performed easily and safely.

It should be emphasized that the technic for the determination of cardiac output by this method is easily and speedily performed and that curve analysis can be delayed for later calculation at one's leisure, if necessary.

Conclusions

1. A method for measuring cardiac output in man by a continuous recording system utilizing the injection of iodinated human serum albumin has been described.

2. Values obtained show an average agreement with those determined by the Fick principle of ± 8.3 per cent over the range of outputs studied.

3. Certain sources of technical error, which may invalidate the determination, have been stressed, the major of which are maintenance of "free" flow during the recording of the primary curve, and accurate delivery of the injected dose upon which calculations are based.

Acknowledgments

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Studies Utilizing the Portable Electromagnetic Ballistocardiograph

III. The Ballistocardiogram in Bundle Branch Block

By HARRY MANDELBAUM, M.D., AND ROBERT A. MANDELBAUM, M.D.

Ballistocardiographic studies were done on 28 subjects with left bundle branch block and on 18 subjects with right bundle branch block. The influence of ventricular asynchronism, and the predominance of left or right ventricular disease, upon the derivation and interpretation of the ballistocardiogram, is discussed. The ballistocardiogram was found to be a valuable objective guide in the detection of subjects whose bundle branch block was not associated with significant heart disease. The ballistocardiogram also provided helpful confirmatory evidence of coronary artery or hypertensive heart disease when this was the suspected or certain diagnosis in subjects with bundle branch block.

THE finding of bundle branch block in the electrocardiogram presents a clearly defined abnormality whose significance must be carefully evaluated by the clinician. When bundle branch block is discovered in a patient who has definite evidence of heart disease, many clinical studies have shown that the outlook for life expectancy is poor.[1–5] In sharp contrast, are statistics which were obtained from medical observation of subjects who were not suspected of having heart disease, and in whom bundle branch block was an unexpected finding.[6–8] In a 20 year observation period of life insurance applicants, Rodstein and coworkers[6] found that there was an excellent outlook as to life span in subjects with bundle branch block who showed no clinical evidence of heart disease; these constituted 50 per cent of the entire group, and the average age of discovery of bundle branch block was 48 years.

It may be assumed, therefore, that bundle branch block may be indicative of only a small scar in the conduction system of a person with a good life span expectancy, rather than always be regarded as a sign of advanced heart disease. The meaning of bundle branch block in each particular case is related only to the extent of the underlying myocardial disease.[9] After demonstrating the existence of bundle branch block, the electrocardiogram can offer little assistance in determining the significance of the finding. A complete history together with the physical examination of the patient is, of course, the basic method for detecting heart disease. A reliable objective guide in determining the extent of disease, if present, in a case of bundle branch block, is the heart size as shown by roentgen examination. Studies[3, 4, 5] of hospitalized patients, based upon duration of life and postmortem findings, have shown that cardiac enlargement in the presence of bundle branch block is a reliable criterion of extensive myocardial disease, and indicates a poor prognosis.

Since the ballistocardiogram has been shown to be valuable in estimating the extent of functional myocardial impairment in coronary artery and hypertensive heart disease,[10–15] it is reasonable to expect that the ballistocardiogram will provide another objective means of evaluating the cardiac status of persons with bundle branch block.

Before application of the ballistocardiograph to the study of bundle branch block, the problem of ventricular asynchronism in bundle branch block and its possible relationship to the derivation of the ballistocardiogram must be clarified. Through the use of roentgenkymographic studies of the pulmonary arterial and aortic pulsations, and optical records of cardiac apex thrust, Wolferth[16] and Braun-Menendez[17]

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have adequately demonstrated asynchronism in the time of ventricular ejection in bundle branch block. With the electrokymogram, Ellinger[18] has confirmed these findings and has calculated the maximum time of ventricular asynchronism to be .05 second in right bundle branch block and .07 second in left bundle branch block. Studies on humans,[18] as well as on dogs,[19] have demonstrated that some degree of ventricular asynchronism is the rule in the majority of normal hearts. In 33 of the normal young adults studied by Ellinger,[18] the left ventricular ejection led by .01 to .03 second; in 21, the right ventricular ejection came first by .01 to .03 second; and in 14, synchronous ventricular ejection was present. Since normal ballistocardiograms were found in all of a group of young normal subjects,[13] this degree of ventricular asynchronism up to .03 second does not apparently affect the ballistocardiogram.

What of the effect of the extremes of ventricular asynchronism which have been found to be up to .07 second? This degree of asynchronism, while not the rule in bundle branch block,[17, 18] probably does not cause an appreciable effect on the ballistocardiographic pattern. Theoretically, extremes of ventricular asynchronism may cause the appearance of notched J waves.[20] In our study of 46 cases of bundle branch block, the normal ballistocardiograms which were recorded revealed nothing unusual in their configuration although many were obtained from subjects who had extremes of QRS widening. This agrees with Starr's reports.[20]

Beside the asynchronism of ejection time, functional ventricular asynchronism due to predominant left or right ventricular disease has been shown to be present in most cases of bundle branch block associated with myocardial disease.[5] Yater[21] has demonstrated that while both bundles are usually involved by disease, cases of bundle branch block associated with coronary artery or hypertensive heart disease reveal pathologically that the left ventricle is predominantly scarred and hypertrophied. In a similar fashion, the right ventricle is predominantly diseased when mitral valve or pulmonary disease is present.[5, 21] The asymmetric weakening of the force of ejection, especially when the left ventricle is predominantly diseased, will result in markedly abnormal ballistocardiograms. Starr[22] has shown that the HIJK complex actually records cardiac ejection velocity rather than cardiac output, and results from a summation of the forces produced by the right and left ventricle. In his cadaver experiments, Starr has demonstrated that the normal HIJK complex of the ballistocardiogram occurs when the maximum velocity of blood ejection is attained *early* in systole. The double-peaked systolic complexes which have been attributed to asynchronism of ejection time[20, 23] probably result from the lag in ejection force from the diseased ventricle.

Ballistocardiographic Studies in Subjects with Bundle Branch Block

The use of the ballistocardiograph proved valuable in confirming the clinical impression of the presence or absence of heart disease in our 46 cases of bundle branch block, who were observed for periods of 12 to 24 months. All of our subjects were ambulatory and comparatively well at the time of the initial ballistocardiographic evaluation. The electrocardiographic diagnosis of bundle branch block was dependent entirely upon the present accepted criteria[9] as applied to the precordial leads. No cases of Wolff-Parkinson-White pattern were included. The direct portable electromagnetic ballistocardiograph[12] was used in all instances. As a rule, the abnormalities of the ballistocardiogram in patients with bundle branch block associated with hypertensive or coronary artery heart disease were found to be similar to those previously described in these conditions.[11, 12] Abnormalities were classified utilizing the nomenclature of Brown.[11] Low H waves were often found in normal tracings.[24]

Left Bundle Branch Block. There were 28 cases of left bundle branch block: 16 were males; 12 were females. All but nine were over 50 years of age. Of eight subjects who had survived a previous myocardial infarction, satisfactory ballistocardiographic recovery to normal or grade I was recorded in two. Coronary artery disease without an episode of proven myocardial infarction was the clinical diagnosis in five subjects. All five demonstrated ballistocardiographic abnormality suggestive of ex-

tensive myocardial disease. In 10 subjects with hypertension but without angina pectoris, four had ballistocardiograms approaching normal. In no case in which heart disease was detected clinically was a normal ballistocardiographic record found. In the 23 subjects with coronary artery and hypertensive heart disease, x-ray evidence of ventricular enlargement was found in 7 of the 17 cases in which the ballistocardiogram detected serious myocardial damage.

TABLE 1.—*Ballistocardiographic Evaluation of 28 Subjects with Left Bundle Branch Block and 18 Subjects with Right Bundle Branch Block*

Ballistocardiogram	Electrocardiogram	No. of Patients	Per Cent	Sex	Age	Cardiac Diagnosis	Heart Size
Normal at rest and after exercise	Left BBB—3 Right BBB—7	10	22	M—6 F—4	31–40—1 41–50—3 51–60—5 61–70—1	Normotension with no evidence of heart disease—6 Hypertension with no evidence of heart disease—2 Healed myocardial infarct—2	Normal—10 Enlarged—0
Minimal abnormalities at rest or after exercise (Grade I)	Left BBB—7 Right BBB—3	10	22	M—3 F—7	41–50—3 51–60—4 61–70—3	Normotension with no evidence of heart disease—2 Hypertension with no evidence of heart disease—4 Coronary artery disease with no definite infarction—1 Healed myocardial infarct—1 Rheumatic valvular disease—1 Lutembacher, digitalized—1	Normal—8 Enlarged—2
Moderate abnormalities at rest or after exercise (Grade II)	Left BBB—7 Right BBB—0	7	15	M—6 F—1	31–40—1 41–50—2 51–60—1 61–70—3	Hypertension with no evidence of heart disease—1 Myocarditis healed—1 Coronary artery disease with no definite infarction—3 Healed myocardial infarct—2	Normal—7 Enlarged—0
Marked abnormalities at rest or after exercise (Grade III or IV)	Left BBB—11 Right BBB—8	19	41	M—13 F—6	41–50—4 51–60—7 61–70—6 71–80—2	Hypertension with no evidence of heart disease—1 Hypertensive heart disease—5 Coronary artery disease with no definite infarction—7 Healed myocardial infarct—6	Normal—8 Enlarged—11

Of the five other cases of left bundle branch block, two were studied because of pain in the left chest, which was not typical of angina pectoris. All studies of cardiac function in these two patients were normal, and the basal and exercise ballistocardiograms were normal. The final diagnosis in one was radiculitis, and, in the other, gall bladder dyspepsia. One subject was studied as part of a routine preoperative checkup. Another, an elderly man, requested a complete investigation because of weakness and weight loss. The fifth case gave a childhood history of a protracted illness following scarlet fever complicated by myocarditis; no valvular disease was detected.

In only 3 of the 28 subjects were the resting and postexercise ballistocardiograms normal. Two of these subjects had no clinical evidence of heart disease; the other had recovered from a myocardial infarction. In seven subjects, the ballistocardiograms were normal or grade I at rest, and not worse than grade I after exercise. Ten subjects, therefore, or 35.7 per cent of the entire group with left bundle branch block, showed ballistocardiograms which were normal or only slightly abnormal. Of these, 8 were 50 years of age or over. These good ballistocardiographic records correlated well, in each case, with the clinical impression that the patient had good myocardial function in spite of findings of left bundle branch block in the electrocardiogram.

Right Bundle Branch Block. Eighteen cases of right bundle branch block were observed from 12 to 24 months. There were 12 males and six females. Fifteen of the subjects were 50 years of age or older. Eight subjects had markedly abnormal ballistocardiograms. Two of these eight had survived a myocardial infarction. The other six were clinically diagnosed as coronary artery or hypertensive heart disease, one of whom developed a myocardial infarct after his initial study. X-ray studies revealed ventricular enlargement in four of these eight cases. One subject, age 35, who had suffered myocardial infarction two years previous to the present study, demonstrated a normal ballistocardiogram, indicating excellent myocardial function. Six other subjects, none of whom showed any evidence of heart disease, although hypertension was noted in two, had normal ballistocardiograms at rest and after exercise. Three subjects had ballistocardiograms which demonstrated only minimal abnormality: one of these three had essential hypertension; the other two were digitalized patients with compensated valvular heart disease. Ten subjects, or 56 per cent of the entire group with right bundle branch block, had ballistocardiograms which suggested good myocardial function. Six of the 10 were over 55. The good ballistocardiographic records confirmed our impression that no serious heart disease was present in each of these cases, with the exception of the two subjects with compensated valvular heart disease.

In comparing the findings from the right and left bundle branch block groups, the striking observation was that the incidence of coronary artery and hypertensive heart disease was about as frequent in both. All of the serious ballistocardiographic abnormalities were noted in association with these degenerative diseases. Though it is undoubtedly true that the left ventricle bore the brunt of the disease in these cases of right bundle branch block with degenerative heart disease, the right bundle, as has been previously noted,[21] apparently had sufficient involvement to dominate the electrocardiographic pattern. Two cases of valvular disease were found in the right bundle branch block group. In both cases, repeated attacks of congestive heart failure necessitated the establishment of compensation by digitalis, mercurials and sodium restriction. Reestablishment of compensation accounted for the minimal ballistocardiographic abnormalities.[22] Some degree of essential hypertension was noted as the only abnormal finding in the majority of patients in both groups whose ballistocardiograms showed grade I abnormality.

The period of observation of the cases herein reported averaged more than 15 months. Excepting the two patients with valvular disease, all of the subjects whose ballistocardiograms were normal or slightly abnormal have done well. Four, whose activities had been previously restricted because of the electrocardiographic

findings of bundle branch block, have returned to their usual occupations.

Conclusion

The ballistocardiographic evaluation of 28 subjects with left bundle branch block, and 18 with right bundle branch block, has demonstrated the value of ballistocardiography in the clinical appraisal of the patient who is found to have bundle branch block. A markedly abnormal ballistocardiogram served as further proof of advanced myocardial impairment when the diagnosis of coronary artery or hypertensive heart disease was considered likely. In the absence of confirmatory evidence of heart disease, the abnormal ballistocardiogram served as a valuable guide in cases in which coronary artery disease was suspected.

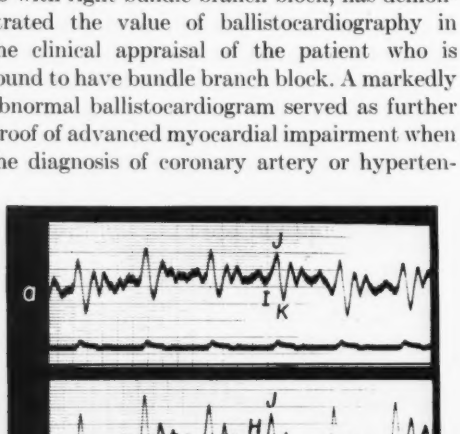

Fig. 1. Ballistocardiograms and electrocardiograms of case 1. See text.

In 58 per cent of the cases with markedly abnormal ballistocardiograms, teleoroentgenograms failed to show enlargement of the heart.

The finding of a normal ballistocardiogram in the presence of bundle branch block in subjects over 50 years of age provided the only objective means at the disposal of the clinician to assure himself as well as the patient of a well functioning heart despite the abnormal electrocardiogram.

Illustrative Cases

Left Bundle Branch Block

Case 1, Figure 1. M. H., female, age 60; normotensive. The patient was subject to recurrent attacks of dyspepsia due to gall bladder dyskinesia. In May, 1950, her husband died of cancer of the lung. Shortly thereafter, she developed chest pain. She consulted a physician who discovered left bundle branch block. She was ordered to bed and digitalis and sedatives were prescribed. Finding no relief, she discontinued all medication after two weeks.

She was examined August 6, 1950; she weighed 127 pounds; the B.M.R. was plus 11 per cent; the blood pressure was 130/80. Examination of the heart and lungs revealed nothing abnormal. X-ray of the chest showed a normal cardiac silhouette. Spondylitis and scoliosis of the cervicodorsal spine were found.

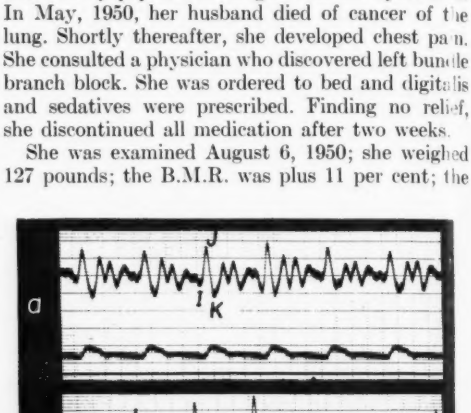

Fig. 2. Ballistocardiograms and electrocardiograms of case 2. See text.

Ballistocardiogram: (a) basal; normal for age 60; (b) exercise test*; normal response, with increased amplitude of complexes.† H waves are low.

Electrocardiogram: (Lead I; Lead III; V_1; V_6) characteristic of left bundle branch block.

With reassurance that no serious heart disease was present, this patient has done well with no

* Exercise test: Unless otherwise stated, the patient performed ten trips on the two-step platform.

† The upper channel in each figure represents the ballistocardiogram; the lower channel, the concomitant tracing taken from the left radial pulse. The J wave is recorded at the apex of the radial pulse.

limitation of activity. Chest pain disappeared after orthopedic care of the spondylitis and scoliosis.

Case 2, Figure 2. B. S., female, age 50. This patient had hyperthyroidism in 1946 and was treated successfully with x-ray therapy. There has been no recurrence since. She has suffered repeated attacks of dyspepsia in the last few years. X-rays examinations of the stomach, intestines and gall bladder were reported as negative. In July, 1950, after eating a very heavy meal, she noted the occurrence of sharp pain over the left breast area which lasted ten minutes. Relief was obtained by belching. There has been no recurrence since. She visited her doctor the next day and in the course of a complete examination, the electrocardiogram showed left bundle branch block. It was felt advisable to put her to bed. However, after two weeks, she insisted that she was not ill and requested consultation by a cardiologist. He felt that it was wisest to have her spend another two weeks in bed.

Mrs. B. S. was examined in October, 1950. There were no subjective complaints. Her weight was 125 pounds; the blood pressure was 125/75 and the B.M.R. was plus 6 per cent. Examination of the heart, lungs and abdomen was negative. Teleoroentgenogram showed the heart to be of normal size and form. Electrocardiogram: (V_1) showed left bundle branch block.

Ballistocardiogram: (a) basal; normal complexes; (b) exercise test; grade I respiratory variation. Short HIJ may be noted in the second complex. H waves are low in amplitude in (a) and (b).

These ballistocardiograms of a normal record at rest with grade I abnormality after moderate exercise we have learned to correlate with minimal functional myocardial impairment, carrying a good prognosis.[25] We assured this patient that in her instance the finding of bundle branch block did not indicate serious heart disease. With no restriction of activity, she has done well since.

Case 3, Figure 3. J. S., female, age 42. Hypertension and albuminuria complicated her second pregnancy in 1938. She was well until 1946 when recurrent headaches led her to seek medical advice at the Hypertension and Nephritis Clinic of The Jewish Hospital of Brooklyn. In 1946, her blood pressure ranged from 180/100 to 200/110. The heart was of normal size and the electrocardiogram showed left ventricular hypertrophy. In 1949, the eyegrounds were grade II. The heart was of normal size. The electrocardiogram was typical of left ventricular "strain pattern." In 1951, her blood pressure ranged between 160/90 and 190/100. She had no complaints. The cardiac silhouette showed the characteristic form of left ventricular hypertrophy; the total diameter was not increased.

Ballistocardiogram: (a) basal; short HIJ, deep K pattern; (b) exercise test; good myocardial response as shown by increased amplitude of complexes and less shortening of the HIJ. H waves are low.

Electrocardiogram: (Lead I; Lead III; V_1; V_6) characteristic of left bundle branch block.

The resting ballistocardiogram, in this instance, demonstrates the diminished HIJ with deep K pattern, which we see in almost every case of hypertension in which there is left heart involvement. The good response to exercise indicates adequate myocardial function and correlates well with the fact that this patient had no cardiac complaints, and that the x-ray showed no evidence of an enlarged heart. The ballistocardiographic findings here more clearly reflected her clinical state than did the successive progressive changes in the electrocardiograms.

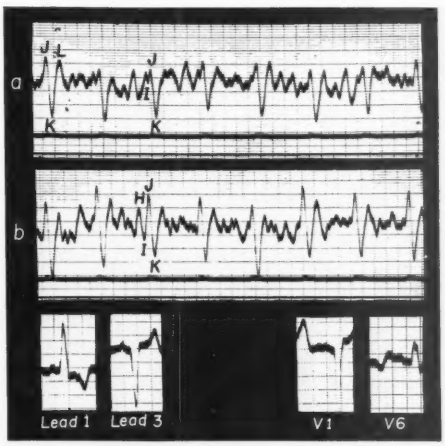

FIG. 3. Ballistocardiograms and electrocardiograms of case 3. See text.

Right Bundle Branch Block

Case 4, J. G., male, age 42. Because of the death of an associate, this patient requested a complete checkup. He had no complaints. His weight was 178 pounds. The blood pressure was 140/80 and the basal metabolic rate was minus 9 per cent. Examination of the heart and lungs showed nothing abnormal. Teleoroentgenogram was negative. The electrocardiogram showed the characteristic findings of right bundle branch block. The ballistocardiogram was normal at rest and after exercise.

Because the physical examination revealed nothing abnormal and because the ballistocardiograms, at rest and after exercise, were normal, the patient was not told of the electrocardiographic abnormality.

Case 5, Figure 4. M. I., male, aged 60. Asymptomatic hypertension has been present for at least 10 years. His blood pressure ranged between 160/100 and 220/115. Since May, 1951, he developed angina on effort. Paroxysmal nocturnal dyspnea has occurred several times in the last 12 months.

October 6, 1951, his weight was 170 pounds; blood

pressure was 205/115; and the basal metabolic rate was minus 9 per cent. Examination of the heart revealed a grade II systolic murmur at the apex and a split second sound. A_2 was greater than P_2. X-ray examination showed the heart to be enlarged in its transverse diameter, and the aorta to be tortuous and prominent.

Ballistocardiogram: (a) basal; fused HIJ waves are common; note prominence of L waves; (b) exercise test (eight trips); the amplitude is not increased; fused HIJ waves and tall L waves dominate the tracing. After eight weeks of digitalis therapy, (c) basal; resembles "a"; (d) exercise test (eight trips) marked improvement noted in amplitude of HIJ complexes.

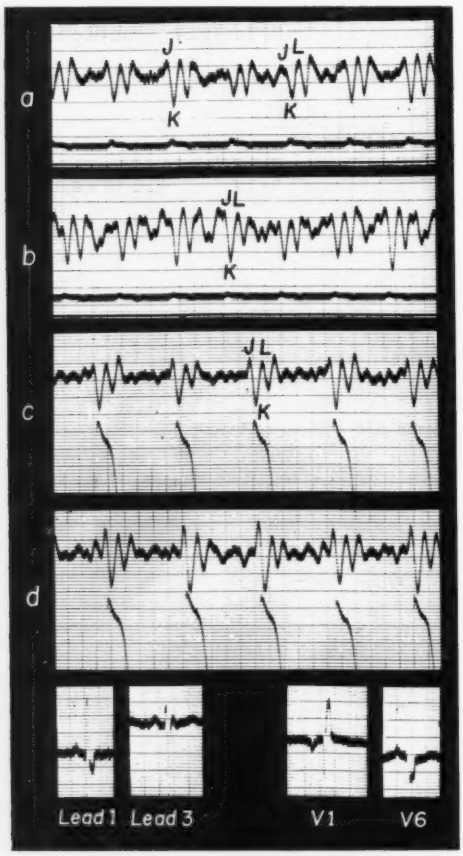

FIG. 4. Ballistocardiograms and electrocardiograms of case 5. See text.

Electrocardiogram: (Lead I; Lead III; V_1; V_6) demonstrated right bundle branch block.

The grade II basal and grade III exercise ballistocardiograms confirmed the clinical impression that serious heart disease was present. No further episodes of dyspnea occurred after institution of digitalis therapy and salt restriction.

Case 6, Figure 5. L. W., male, aged 51. Hypertension has been present for several years. He has noticed angina pectoris on effort and after heavy meals during the last two years.

November 16, 1950, he weighed 171 pounds; the blood pressure was 210/130; basal metabolic rate was plus 14 per cent. A grade II aortic systolic murmur was noted; roentgenogram showed the heart to be enlarged to the left with a prominent aortic arch.

Ballistocardiogram: (a) basal; the low amplitude and lack of definitiveness permits classification of grade IV; (b) exercise test (seven trips); grade III.

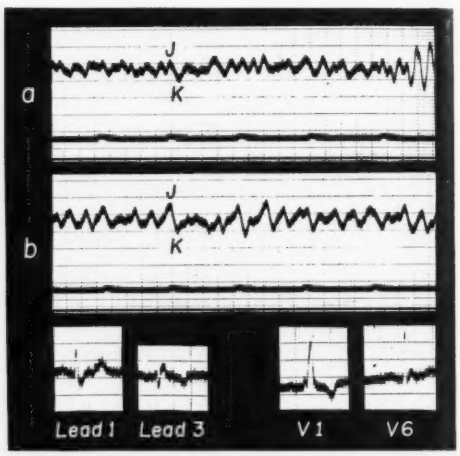

FIG. 5. Ballistocardiograms and electrocardiograms of case 6. See text.

The markedly abnormal ballistocardiograms indicate that the bundle branch block in this 51 year old male is associated with advanced myocardial disease.

Electrocardiogram: (Lead I; Lead III; V_1; V_6) showed the characteristics of right bundle branch block.

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Relationship between Ballistocardiographic Forces and Certain Events in the Cardiac Cycle

By Oscar Tannenbaum, M.D., Jerome A. Schack, M.D., and Harry Vesell, M.D.

The temporal relationships of the various waves of the ballistocardiogram have been studied by means of simultaneously recorded electrocardiograms, femoral pulses, and electrokymograms of the great vessels and heart chambers. A modification of the Dock type of electromagnetic, undamped, direct ballistocardiograph has been employed in this study of 23 normal individuals. The total duration of mechanical systole in the great vessels has been found to correspond closely to the H–L interval. The HIJKL complex of the ballistocardiogram appears to be entirely related to the events of ventricular systole. The M, N and O waves represent after-waves occurring during diastole.

Henderson[1] studied the recoil curves of the heart and circulation as early as 1905 and attempted to derive cardiac output. For many years, little was done with this method until Starr[2] modified the apparatus and suggested its use not only for the measurement of cardiac output but also as a clinical tool in evaluation of the functional status of the heart. Starr and his co-workers extensively investigated ballistocardiography and described the findings in both health and disease. However, because of the bulkiness of the equipment, the method did not gain widespread clinical application until recently when Dock and Taubman[3] described a simple, portable and easily constructed instrument which recorded the ballistic curve directly from the body.

The origin and naming of the various waves of the ballistocardiogram was described by Starr and his associates.[2] Nickerson,[4] using a low frequency critically damped instrument studied the origin of the H and K waves by means of mechanical models and clinical observation. Hamilton[5] investigated the ballistocardiographic forces in relation to cardiac ejection curves and came to the conclusion that the calculation of cardiac output by means of the ballistocardiogram was empiric and should be considered as comparative rather than absolute. He did feel, however, that qualitative study of the ballistic pattern might be of value in clinical medicine.[6]

With the advent of electrokymography in a stable, practical form,[7] an excellent means of studying the temporal relationship of the ballistocardiogram to the events of the cardiac cycle was established. We have studied the relationship of the ballistocardiographic waves to the electrokymogram in the normal state.

Material and Methods

Twenty-three normal subjects ranging in age from 18 years to 38 years were selected. Ten were male and 13, female. The usual clinical criteria were used to judge these subjects normal: namely, history, physical examination, electrocardiogram, x-ray films of the chest, urinalysis and hemogram. The studies were all carried out at the same time of the day, usually three hours after eating. No attempt was made to secure a strict basal state. The following four events were simultaneously recorded on a four-channel, direct-writing oscillograph, the characteristics of which have been described elsewhere[8]: (1) the electrocardiogram lead I, (2) electrokymogram, (3) ballistocardiogram, (4) femoral sphygmogram. All tracings were taken with the subject in the recumbent position and with the breath held in midinspiration. Electrokymograms were obtained in the postero-anterior projection. The following points were selected: (1) midportion of the aortic knob, (2) pulmonary artery at the left cardiac border, (3) high left ventricle, (4) left ventricle near the apex. All recordings were made at a paper speed of 25 mm. per second.

The electrocardiogram was selected as the con-

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mon reference point for the timing of the various phases of the cardiac cycle. It was felt that the electrocardiogram was subject to little variation and did not have the lag factor present in the carotid sphygmogram.[9]

The electrokymograph was of the type described by Henny and Boone[7] consisting of a 931A RCA photocell, a high voltage power supply and a 120 cycle filter. The x-ray generator was of the full wave rectification type and was operated at 5 milliamperes and between 60 and 75 kilovolts, depending on the thickness of the subject. The movements were recorded with a delay of 0.02 second which is inherent in the equipment and presumably due to the filter.[11] Repetitive tracings taken from identical points on the cardiac border in the same individual on successive days were found to be similar in contour and temporal relationships. However, the amplitude of these successive tracings was not constant. This difficulty has been encountered by other workers,[11, 14, 15] and is characteristic of the method.

The ballistocardiograph was of a modified electromagnetic (variable reluctance) type as described by Dock. This inscribed curves of the type obtained by the Starr table.[12] Our modification consisted of the following: the coil consisted of a core of soft iron measuring 15 mm. by 10 mm. by 2 mm. and was wound in layers with 4,000 turns of number 40 enameled wire. This was connected to the recording galvanometer through a filter which consisted of a 2.5 millihenry choke in each lead and a 25 microfarad condenser across the coil. The coil was mounted on a suitable support such as a standard laboratory stand. It was placed exactly 10 mm. from the Alnico V magnet which is mounted on a wooden bar that is secured to the shins of the subject by means of elastic bands. The magnet measured 1 inch by 1 inch by ¼ inch. The sensitivity of the galvanometer was adjusted so that 1 millivolt produced a 1 cm. deflection.

By introducing the iron core the sensitivity of the pickup system was increased manyfold, and thus we were able to employ a large gap between the coil and the magnet to facilitate standardization. A standard gap of 10 mm. was employed, thus allowing comparison of the amplitude of records. The filter was used to attenuate the high frequency vibrations due to muscle tremors as well as much of the stray alternating current present. The filter introduced no lag. This was determined in the following manner: The coil was mounted on its support 10 mm. from the magnet which was attached to its wooden mount. A silver contact was fixed about 6 mm. from the magnet. A similar silver contact fixed to a swinging arm acted as a switch to close a circuit which introduced a 1 millivolt signal into one channel of the galvanometer. The other channel of the galvanometer was connected to the pickup coil. Thus when the swinging arm struck the contact on the mount of the magnet, two signals were simultaneously introduced, one mechanical and the other electrical. These were recorded at a speed of 50 mm. per second. The take-off points on the two curves so inscribed were exactly simultaneous. A similar procedure was employed with the subject connected and the blow delivered to the shoulder. No lag was observed. With this system repeat tracings taken at weekly intervals upon the same subject were identical in all respects. Thus the variable reluctance direct ballistocardiograph may be expected to yield completely reproducible tracings when used under the conditions of standardization described.

The femoral pulse was recorded by means of a piezo-electric pickup as described by Miller and White[13] which is free of lag.

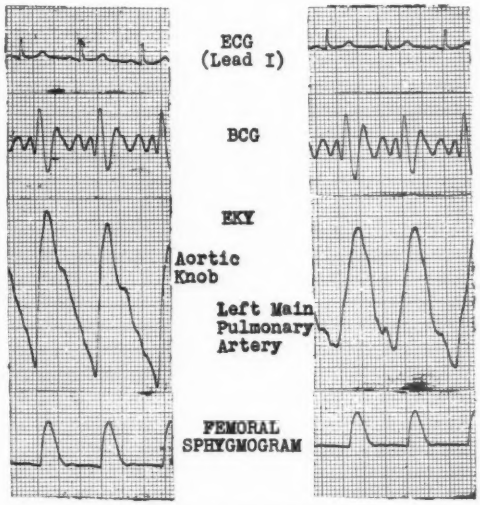

FIG. 1. Simultaneous recording of the electrocardiogram, ballistocardiogram, electrokymogram, and femoral sphygmogram; paper speed 25 mm. per second; time lines are 0.04 second apart. (See text for discussion.)

All deflections obtained were related to the onset of the QRS complex of the electrocardiogram. Measurements were compared in cycles of equal duration in a given subject. The following intervals of the electrocardiogram were measured: R-R, P-R, QRS, and Q-T. The ballistocardiograms were analyzed as follows: the onset ("h")* and the peak of the H wave to the peaks of each of the succeeding waves (for example, I, J, K, L) were measured. The time interval from the initial QRS wave of the electrocardiogram to the peak of each ballistic wave was measured.

The points measured on the electrokymogram were the conventional ones described by Boone

* Onset of H wave is designated "h".

and co-workers,[14] Heyer, [15] Engström and co-workers,[9] and Anderson.[16] In the great vessels (pulmonary artery at the left cardiac border and the aortic knob) the rapid ejection phase of the ventricles was measured from the beginning of the rise of the anacrotic limb to the peak. From this point to the incisura was considered the period of reduced ejection. Total ejection time was represented by the sum of the rapid and reduced ejection phases. The isometric contraction phase was not measured because of the difficulty of delineating this portion of the curve.[15] The ventricular electrokymogram was similarly analyzed. Because of the marked variability in these curves, we were unable to draw any satisfactory conclusions from them. Similar difficulties have been encountered by other observers.[17, 18] We have consequently utilized the pulmonary artery and aortic curve. The validity of these has been substantiated by comparison with intraluminal pressure curves.[8, 19] The various points on the curves of the electrokymogram were related to the onset of the initial QRS wave of the electrocardiogram.

In relating the electrokymographic curves to the ballistocardiogram, the factor of lag due to transmission time of the pulse wave in the great vessels had to be considered. The transmission time from the ascending aorta to the aortic knob has been reported by various observers to be 0.015 second.[9, 14] The lag factor for the pulmonary artery is of a similar degree. We have determined this to be 0.015 second by means of successive recordings of the electrokymogram of the pulmonary artery near the root in the right anterior oblique and at the left cardiac border in the postero-anterior projection.

The femoral pulse curve was related to the initial QRS of the electrocardiogram and to the waves of the ballistocardiogram.

Results

1. Inter-relation of the Various Waves of the Ballistocardiogram. Table 1 summarizes the relationship of the various waves of the ballistocardiogram to each other. It will be noted that these relationships were quite constant and varied little from the mean. Comparison of the H–I, I–J, J–K, and K–L intervals with cycle length (R-R) revealed no significant correlation at the cardiac rates observed.

2. Relation of the Ballistocardiogram to the Electrocardiogram. The interval between the onset of the P wave of the electrocardiogram and the beginning of the H wave ("h") of the ballistocardiogram varied from 0.12 second to 0.20 second with an average of 0.17 second (see table 2).

The relationship of each of the deflections of the ballistocardiogram to the onset of electrical systole was constant. Table 1 relates the onset of electrical systole to peaks of the various ballistic waves. It will be noted that the total variations of the Q–I, Q–J, and Q–K intervals did not exceed 0.08 second. Q–L had a much wider range, 0.17 second. Q–H had the least variation, 0.05 second.

Table 1.—*The Relationship of the Various Waves of the Ballistocardiogram to Each Other and to the Onset of Electrical Systole*
(Time in Seconds)

	R-R	hI*	HI	IJ	JK	KL	Qh†	QH	QI	QJ	QK	QL
Min.	0.58	0.08	0.04	0.04	0.06	0.05	0.01	0.04	0.10	0.16	0.26	0.29
Max.	1.12	0.14	0.08	0.08	0.12	0.12	0.06	0.12	0.18	0.24	0.34	0.46
Mean	0.74	0.11	0.05	0.06	0.09	0.09	0.04	0.09	0.14	0.21	0.30	0.37
Sigma	0.13	0.018	0.014	0.01	0.015	0.019	0.018	0.019	0.019	0.023	0.027	0.042

* Denotes onset of the H wave to the peak of I. All others designate the peak of the ballistic wave.
† Denotes Q wave when present or onset of R to onset of the H wave of the ballistocardiogram.

3. Relation of the Ballistocardiogram to the Electrokymogram. The onset of the anacrotic limb of the aortic electrokymogram was almost synchronous with the peak of the H wave. The interval was −0.02 second, ±0.026 second. It is of interest to note that 14 of the 22 measurements relating the peak of the H wave to the onset of the anacrotic limb of the aortic electrokymogram occurred from −0.02 to +0.02 second. The onset of the anacrotic limb of the pulmonary artery electrokymogram was more nearly synchronous with the onset of the H wave ("h") than with the peak of the H wave of the ballistocardiogram. This interval was 0.006 second, ±0.03 second.

The peak of the anacrotic limb of the aortic

electrokymogram corresponded in time to the peak of the J wave of the ballistocardiogram with a mean of 0.005 second, ±0.01 second. A similar time relationship existed between the peak of the anacrotic limb of the pulmonary artery electrocardiogram and the J wave with a mean of −.005, ±0.04 second.

The relationship of the peak of the L wave of the ballistocardiogram to the incisura of the aortic wave of the electrokymogram ranged from plus to minus 0.05 second, with two exceptions. The mean was 0.005 second, ±0.06 second. When the peak of the L wave was related to the incisura of the pulmonary artery electrokymogram from 0.10 second to 0.24 second, with a mean of 0.13 second and 0.17 second respectively. The H–J interval (0.08 to 0.14 second, mean 0.11 second) was in close agreement with the duration of the phase of rapid ejection. The reduced ejection phase in the aortic electrokymogram and pulmonary artery electrokymogram agreed closely with the measurements of the J–L interval which ranged from 0.13 second to 0.24 second with an average of 0.17 second.

5. Relation of the Femoral Sphygmogram to the Ballistocardiogram and the Aortic Electrokymogram. The onset of the ascending limb of the femoral pulse wave was almost synchronous with the peak of the J wave of the ballistocardiogram. The difference in time between these two was only 0.00 second to 0.05 second, with an average of 0.02 second. The peak of the femoral pulse wave coincides roughly with the bottom of the K wave of the ballistocardiogram, with a difference of 0.01 second to 0.08 second, average 0.03 second. The time interval from the onset of the anacrotic limb of the aortic electrokymogram to the onset of the femoral pulse wave ranged from 0.075 second to 0.135 second, with an average of 0.11 second in 16 of the subjects studied. This interval was in close agreement with the H–J time of the ballistocardiogram, which ranged from 0.08 second to 0.14 second, average 0.13 second.

TABLE 2.—*The Relationship of Certain Ballistocardiographic Waves to the Ejection Phase in the Great Vessels Electrokymogram*
(Time in Seconds)

	"h"*			"H"†		"J"‡		"L"§	
	Onset P Wave ECG	Onset Aortic Eject.	Onset Pul. Art. Eject.	Onset Aortic Eject.	Onset Pul. Art. Eject.	Peak Aortic Eject.	Peak Pul. Art. Eject.	Dicrot. Notch Aorta	Dicrot. Notch Pul. Art.
Min.	−0.12	−0.005	−0.045	−0.065	−0.095	−0.055	−0.065	−0.115	−0.075
Max.	−0.20	0.085	0.045	0.045	0.005	0.065	0.105	0.145	0.065
Mean	−0.17	0.04	−0.006	−0.02	−0.06	0.005	−0.005	0.005	−0.02
Sigma	0.02	0.024	0.03	0.026	0.05	0.01	0.04	0.06	0.04

* "h" denotes the onset or foot of the H wave.
† "H" denotes the peak of the H stroke.
‡ "J" denotes the peak of the I–J stroke.
§ "L" denotes the peak of the K–L stroke.
Negative sign signifies the event precedes the reference wave of the ballistocardiogram; positive sign signifies the event follows the reference wave of the ballistocardiogram in time.

curve of the electrokymogram, the interval was found to be −0.02 second, ±0.04 second.

4. Relation of the Ballistocardiogram to the Ventricular Ejection Phases in the Great Vessel Electrokymograms and to Electrical Systole. Comparison was made between electrical systole (Q-T interval), mechanical systole as reflected in the electrokymograms of the great vessels, and the h-L interval of the ballistocardiogram. The mean Q-T interval was 0.31 second. The mean mechanical systole of the ventricle as derived from the aortic electrokymogram was 0.30 second, and as derived from the pulmonary artery electrokymogram was 0.34 second. The mean h-L interval was 0.34 second.

The rapid ejection phase of the aortic electrokymogram ranged from 0.08 second to 0.20 second, and that of the pulmonary artery elec-

Discussion

The H wave is the initial headward deflection of the ballistocardiogram. Various theories of its origin have been advanced. Hamilton[5] has related it to the apical thrust and isometric contraction of the ventricles. Nickerson,[4] on the other hand, felt it was produced by auricular contraction, whereas de Lalla and Brown[20] have postulated that its origin was due to the deceleration of the auricular impulse wave by venous arches in the neck, or skull, or both. In our studies the onset of ventricular ejection as indicated by the aortic electrokymogram occurred on the average 0.02 second before the peak of the H wave of the ballistocardiogram, whereas the onset of the H wave ("h") of the ballistocardiogram occurs 0.04 second before the onset of ejection into the aorta. From this data one can infer that the peak of the H wave corresponds to the onset of the rapid ejection phase of the ventricle and that the onset of the H wave ("h") probably is associated with isometric contraction of the ventricle.

In previous studies in man and animal[21] the isometric contraction phase has been found to average about 0.05 second. This would confirm the impression that the period between the onset of the H wave ("h") and the peak of the H wave corresponds to the period of isometric contraction of the ventricle. The average time between onset and peak of the H wave of the ballistocardiogram is about 0.05 second (range 0.04 second to 0.08 second). Furthermore, the onset of the P wave of the electrocardiogram to the onset of the H wave ("h") of the ballistocardiogram varied from 0.12 second to 0.20 second, with an average of 0.17 second (see table 2), which is consistent with the findings of Coblentz and co-workers[22] who, using direct catheter studies, found that the onset of the P wave of the electrocardiogram and the beginning of auricular systole varied from 0.05 second to 0.12 second (0.09 second, average) in the normal subject. This would indicate that the H wave was not produced by auricular contraction and that the formation of the H wave is a result of ventricular function.

The peak of the aortic and pulmonary artery curves of the electrokymogram corresponded closely in time to the peak of the J wave of the ballistocardiogram, the difference on the average being only from plus to minus 0.005 second. Thus the peak of J wave corresponds to the end of rapid ejection of both ventricles. When one compares the time from the peak of the H wave to the peak of the J wave of the ballistocardiogram with that of the rapid ejection phase of the aortic electrokymogram, there is rather close correlation (see table 3). One will note that the H–J time ranged from 0.08 second to 0.14 second, with an average of 0.11 second, which was equal to the time of rapid ejection of the left ventricle as measured in the aortic electrokymogram. The latter had an average time of 0.13 second with a range of 0.08 second to 0.20 second. This is in keeping with the

Table 3.—*The Relationship of the Ballistocardiogram and the Ejection Phases in the Great Vessels* (Time in Seconds)

	Rate	"Total Ejection"*				"Rapid Ejection"†			"Reduced Ejection"‡		
		ECG	BCG	EKY		BCG	EKY		BCG	EKY	
		Q-T	h-L	Aorta	Pul. Art.	H-J	Aorta	Pul. Art.	J-L	Aorta	Pul. Art.
Min	0.58	0.22	0.27	0.20	0.20	0.08	0.08	0.10	0.13	0.12	0.08
Max	1.12	0.40	0.42	0.40	0.41	0.14	0.20	0.24	0.24	0.25	0.30
Mean	0.74	0.31	0.34	0.30	0.34	0.11	0.13	0.17	0.17	0.16	0.17
Sigma	0.13	0.04	0.036	0.053	0.056	0.014	0.033	0.036	0.027	0.045	0.051

* From onset anacrotic limb of great vessel electrokymogram to the dicrotic notch (hence includes protodiastole).

† From onset anacrotic limb of great vessel electrokymogram to peak of anacrotic limb great vessel electrokymogram.

‡ From peak of anacrotic limb great vessel electrokymogram to dicrotic notch.

concept that the H–I stroke accompanies early ventricular ejection,[23] and that the peak of the J wave demarcates the end of the rapid ejection phase of the ventricle.

The reduced ejection phase of the left ventricle as measured in the electrokymogram of the aorta ranged from 0.12 second to 0.25 second, with an average of 0.16 second. As has been shown previously, the peak of the J wave occurred at the same time as the peak of the anacrotic limb of the aortic curve of the electrokymogram, and the peak of the L wave of the ballistocardiogram, on the other hand, occurred at the same time as the incisura. Hamilton[5] noted this relationship of the peak of the L wave to the incisura of the central pulse. When the J–L time of the ballistocardiogram is compared with the reduced ejection phase of the great vessels there is close correlation (see table 3). From these observations the L wave thus represents in reality a forced movement and not a passive after-vibration. It consistently occurred at the incisura, which for all intents and purposes is part of effective ejection phase of the ventricle (including protodiastole).[14]

It should be emphasized that the onset of ventricular ejection occurred at the peak of the H wave of the ballistocardiogram and ended at the peak of the L wave (opening and closure of the semilunar valve). The rapid ejection phase corresponds to the H–J interval and the reduced ejection to the J–L interval. Thus the H–L interval serves as a measure of ventricular systole. As might be expected, this H–L interval varies little with increase in cardiac rate, the changes in rate affecting almost solely the M, N, O interval, or diastole.

Brown and de Lalla[24] measured the H–K time and found it proportional to the size of the subject, and from this observation have stated that it is proportional to the transmission time of the aortic wave. Hamilton[5] found that the peak of the femoral pulse is on the average coincident with the valley of the K wave of the ballistocardiogram. He could not change this relationship by occluding the arteries of the legs with pressure cuffs. Nickerson[4] found a change in the K wave in subjects with coarctation of the aorta and felt that the shortening of the aorta or constriction of this vessel led to a disappearance of the K wave. Further, he placed cuffs on the thighs and raised the pressure therein to above systolic levels for a period of 15 minutes, then released the constriction, causing a reactive hyperemia of the lower extremities. This produced an increase in the slope of the I to J movement of the ballistocardiogram and a decrease in the relative depth of the K wave.

In our studies we have measured the interval from the onset of ventricular ejection (on the aortic electrokymogram) to the onset of the femoral pulse wave, and have found an average time of 0.11 second, which compares with the transmission time of the pulse wave observed by others.[25] Furthermore, this transmission time coincides with the H–J time (see table 4). The H–K time is almost twice as long (average 0.20 second). The H–K time is equal to the time of transmission of the pulse wave from the root of the aorta to the onset of the tibial pulse. The K wave may thus very well represent the reflection of the blood column in the arterioles in the distal part of the lower extremities. This may explain the increased I–J stroke and diminished depth of the K wave reported by Nickerson[4] after induced reactive hyperemia of the lower extremities.

TABLE 4.—*The Relationship of the Femoral Pulse to the Ballistocardiogram and the Onset of Aortic Ejection of the Electrokymogram—16 Subjects*
(Time in Seconds)

	Ao to F.P.*	F.P. to J†	H-J
Min.	0.075	0.00	0.08
Max.	0.135	0.05	0.14
Mean	0.109	0.02	0.13
Sigma	0.016	0.016	0.023

* Denotes the onset of aortic ejection to the onset of the femoral pulse.

† Denotes the onset of femoral pulse to the peak of the J wave of the ballistocardiogram.

SUMMARY

Simultaneous electrocardiogram, ballistocardiogram, aortic and pulmonary artery electrokymograms and femoral sphygmogram were recorded in 23 normal subjects.

The onset of ventricular ejection occurred at

the peak of the H wave. The onset of the H wave ("h") to the peak of the H wave represented isometric contraction phase of the ventricle. The peak of the J wave occurred at the peak of ventricular ejection phase of the aortic electrokymogram. The peak of the L wave of the ballistocardiogram was coincident with the incisura of the aortic electrokymogram. The rapid ejection phase corresponded to the H–J period and reduced ejection to the J–L period. The H–J time was equal to the transmission time of the pulse wave from the root of the aorta to its arrival at the femoral artery. The K wave may represent reflections of the blood column striking the arterioles in the distal part of the lower extremities.

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Massive Infarction of the Right Ventricle and Atrium

Report of a Case

By EARL A. ZAUS, M.D., AND WALTER M. KEARNS, JR., M.D.

This is a report of a case of massive infarction of the right ventricle and atrium, expanded to include similar cases found in the literature. The clinical manifestations are believed to confirm views expressed by others that peripheral congestive failure is not immediately related to failure of the right ventricle. The diagnostic value of the electrocardiogram in this lesion is examined.

IN a well-reasoned paper in 1949 Starr[1] presented clinical and experimental evidence which disputed the classic view that backward failure of the right ventricle was the sole factor responsible for congestive failure. He and his co-workers[2] had found that complete destruction of the right ventricle in dogs did not produce a rise in venous pressure. This was confirmed by Bakos.[3]

Recently we observed the effects of destruction of the right ventricle in man due to infarction. A report of this case will follow. Included in this study are also 11 similar cases found in the literature. In necropsy material[4] totaling 1651 infarcted hearts* there were only 29 isolated infarctions of the right ventricle. Only four among this group were documented well enough to be used for the purpose of this paper. From other sources[5–11] an additional seven cases were found. The anatomic and clinical features of these cases are summarized in table 1.

CASE REPORT

The patient, a 69 year old white male, was admitted for an attack of precordial pain which had occurred 10 days before admission. Three and one-half months previously he had consulted a physician for severe frontal headaches; a blood pressure of 176/104 was recorded. An electrocardiogram taken at that time is shown in figure 1*A*.

At home the precordial distress had subsided but he was extremely weak and showed cynosis and dyspnea upon exertion, as he refused to stay in bed. At times he was rather stuporous. For one week after the onset he had been completely anuric. Slight swelling of the ankles had been present, clearing on bed rest.

Physical examination in the hospital revealed an acutely ill, stuporous, moderately dyspneic white male, weighing 220 pounds, 62 inches tall, with grade 2 cyanosis, temperature 98.0 F., pulse 56, regular and weak, and a blood pressure of 132/70. The exposed skin surfaces were cold and damp. The jugular veins were moderately distended while the superficial arm veins were in collapse. The sclerae were icteric and the breath ammoniacal. There was dullness, reduced fremitus, and absent breath sounds in the lower right chest posteriorly. Medium moist rales were present in the left base. The heart was enlarged to the left anterior axillary line, the tones distant, but no murmurs or friction rub were heard. There was marked tenderness in the right upper quadrant of the abdomen and a fluid wave was thought to be present. The liver was palpated three fingerbreadths below the right costal margin. There was slight sacral edema.

On the morning of the fourth hospital day, he suddenly became very dyspneic and expired.

Laboratory Findings

The urine showed a specific gravity of 1.010 to 1.014, no sugar, albumin or bile; but 20 to 25 red blood cells per high power field and a 2 plus urobilinogen were found on admission. Twenty-four hour urinary output ranged from 850 to 1200 cc. There were 23,000 white blood cells per cubic millimeter. The Kahn test was negative. Blood chemistry per 100 cc. showed 200.5 mg. glucose, 160 mg. nonprotein nitrogen, 1.48 units of alkaline phosphatase, 156 mg. cholesterol, total protein of 5.9 Gm., 2.8 Gm. of albumin and 3.1 Gm. of globulin. The cephalin flocculation test was plus 2 at the end of 24 hours and plus 3 in 48 hours, and the icteric index was 27. On the third hospital day, the nonprotein nitrogen was 131.5 mg. per 100 cc.

An electrocardiogram taken on the day of admis-

* There may be some duplication of cases in two of these reports[4f and 4j], as both originate from the Massachusetts General Hospital, 1914–1934 and 1926–1945, respectively.

TABLE 1.—*Anatomic and Clinical Findings in Reported Cases of Primary Infarction of the Right Ventricle*

Case and Source	Recent			Old			Description of Coronary Artery Pathology	Electrocardiogram	Clinical Picture
	R	L	S	R	L	S			
1. (5)	A	?	A, P?	0	0	0	Not given.	Q_3T_3 pattern	Not given.
2. (4a)	A P At	?	A	0	0	A	Thrombus in main right overlaying old clot; marked sclerosis of left.	Q_3T_3 pattern	Before attack, 8 months peripheral congestive failure controlled with digitalis and mercurials; infarction followed by pain and dyspnea, fall in B.P.; death 4th day.
3. (6)	A P L	0	A P	0	0	0	Thrombus in main right 2 cm. from ostium extending well into infarcted area; marked arteriosclerosis; left normal.	Q_3T_3 pattern; idioventricular rhythm.	Pain, shock, and severe dyspnea; no peripheral congestive signs; death on 3rd day.
4. (7)	A P	0	A P	0	0	0	Not given.	T_n pattern; QS pattern; S-T segment elevation in $V_1V_2V_3$; RS in V_4 with isoelectric S-T segment; Rs and S-T segment depressed in V_5V_6.	Not given.
5. (4j)	A P L	0	0	0	0	0	Not given.	Q_3T_3 pattern (?)	Not given.
6. (4j)	A P	A	0	A P	0	0	Right orifice does not admit a probe; clots in right descending and left anterior descending.	Early Q_1T_1 pattern: Later Q_3T_3 pattern; idioventricular rhythm.	Not given.
7. (4j)	P L	P	P	0	A L	0	Complete occlusion of right 3 cm. from origin; and also at right margin; narrowing of left anterior descending.	Low voltage; slurred QRS complexes; inverted $T_{2,3}$.	Not given
8. (9)	P L	0	0	0	A P	0	Recent clot in right; marked obliterative sclerosis of all arteries.	Not given.	Not given.
9. (10)	P L	0	0	P L	0	0	Recent and old clots right; sclerosis of all arteries.	Q_3T_3 pattern.	Not given.
10. (11)	P L	0	P	0	A	0	Not given.	T_n pattern	Not given.
11. (8)	P L At	0	0	0	A	0	Congenital single artery arising from right, with anomalous large branch going left, with all branches. Thrombi: large one at bifurcation of main artery occluding the point of origin and partly the anomalous left; another one almost completely occluding the right between its origin and the acute margin of the right side of the heart; third clot producing closure of right branch at posterior interventricular sulcus; atherosclerotic plaques occluding anterior descending branch.	Q_3T_3 pattern; CF_4 shows marked S-T segment depression.	Ashen gray, cold, moist skin; thready pulse; blood pressure 94/52; dyspnea at onset; on second day, anuria, labored breathing, left hemiplegia, cyanosis, stupor, and many basal rales; death on 6th day; autopsy showed passive congestion of liver and lungs; bilateral bronchopneumonia; and arteriolar nephrosclerosis.

Key: A = Anterior wall; P = Posterior wall; L = Lateral wall; At = Atrium; ? = Data indefinite; R = Right; L = Left; S = Septum.

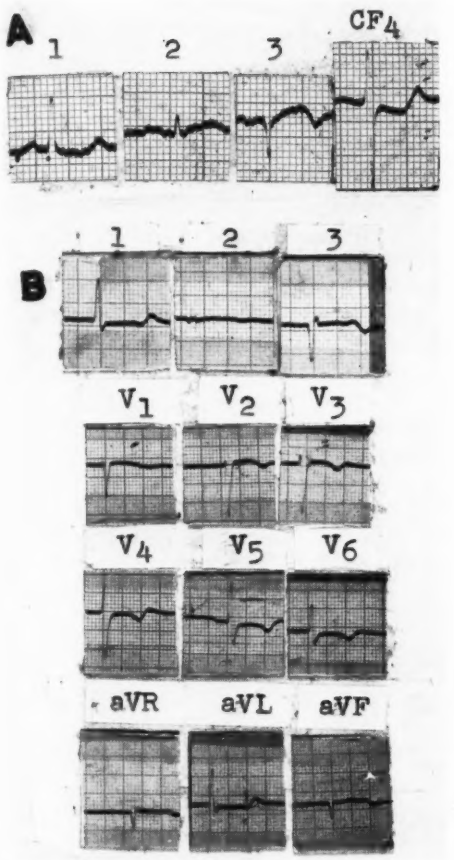

FIG. 1*A*. Tracing taken about three months before terminal attack, suggestive of damage to the posterior wall of the left ventricle.

B. Taken on tenth day of attack: the heart is horizontal with moderate clockwise rotation; idioventricular rhythm with rate of 56 is present; corrected Q-T interval measures 0.447 seconds[26]; the limb leads show a Q_3T_3 pattern; the right-sided precordial leads show an rS complex, plateau-type S-T segment, and T wave inversion; the left-sided leads show an RS complex, depression of the S-T segment, and diphasic T waves with major deflection downward; in aV$_L$ the S-T segment is depressed, while in aV$_F$ there is a QS complex, and depression of the S-T segment and the T wave.

The possible interpretations of these complexes are: (1) left ventricular anteroseptal infarct, (2) hypertrophy-strain pattern of the left ventricle, (3) right ventricular strain pattern with superimposed digitalis* effect, (5) subendocardial infarct of the anterior wall of the left ventricle plus right ventricular strain, (6) anterior pericarditis, (7) anteroposterior infarction of the right ventricle.

sion (figure 1*B*) was interpreted as being indicative of severe myocardial damage.

Postmortem Description

The heart weighed 500 Gm. There was moderate hypertrophy of both ventricles and moderate dilatation of the right ventricle. Almost the entire wall of the right ventricle was occupied by a recent infarct (fig. 2). In addition a small portion of the posterior wall of the left ventricle and interventricular septum was involved. The site of the infarct corresponded approximately to the location of the deep sinospiral muscle and a portion of the adjacent superficial sinospiral bundle. A large mural thrombus occupied the lateral and posterior walls of the right ventricle. There was a recent infarct and mural thrombus of the entire right auricular appendage and a small portion of the adjacent right atrium and the left auricular appendage. Fibrosis from an old infarct was present in the posterior wall and adjacent interventricular septum of the left ventricle. Microscopically, the recent infarcts were judged to be about two weeks old.

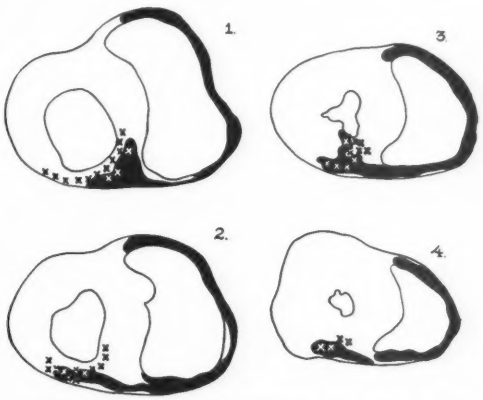

FIG. 2. Diagrammatic representation of the areas of damage in transections of the ventricles, starting at the base and proceeding to the apex (1 to 4 in sequence), showing laminar infarct involving the deep sinospiral muscle in the right ventricle and an isolated portion of the posterior wall of the left ventricle. The areas marked x indicate the site of a healed infarct.

There was marked right coronary artery preponderance. All the coronary arteries showed moderate to marked arteriosclerosis, the smaller left coronary artery and its main branches demonstrating more advanced changes than the large right coronary artery. There was marked narrowing of the lumina of the left circumflex and left anterior

* No glycosides were used in therapy of this patient.

descending arteries. A recent thrombus totally occluded the main right coronary artery for a distance of 8 cm. starting from a point 0.5 cm. distal to the ostium. An old canalized thrombus was present just proximal to the right posterior descending artery and a recent thrombus was present here for a distance of 1.0 cm. Three large branches of the right coronary artery supplying the right ventricle were occluded in their proximal portions by extension of the thrombus in the parent vessel. There was a small patent accessory right coronary artery. The coronary sinus and anterior cardiac veins were patent. There was no gross or microscopic evidence of obstruction of the thebesian or arterioluminal groups of vessels.

The right and left lungs weighed 320 and 260* Gm. respectively. There were recent emboli measuring up to 2.0 cm. in length in the smaller branches of both pulmonary arteries. Both lower lobes contained recent infarcts measuring up to 3 cm. in maximum diameter. Histologically, the lungs showed passive hyperemia, and slight chronic pulmonary emphysema.

The liver weighed 1700 Gm. and showed passive hyperemia. The pancreas showed focal areas of necrosis with acute and chronic inflammation. The spleen weighed 250 Gm. and showed passive hyperemia. The kidneys showed marked arteriolar sclerosis and regenerating tubular epithelium consistent with a diagnosis of a lower nephron lesion.

Dicussion

Pathologic anatomy. Various anatomic[4c, 12–16] and physiologic† reasons may account for the rarity[20–22] of isolated right ventricular infarction; either the right ventricle is favored with a better collateral circulation, or damage to it requires greater restriction in blood supply than is necessary to produce ischemic death in the left ventricle. The status of the coronary circulation in this and in cases 4, 5, 8, and 9 (table 1) suggest the importance of the latter factor.

Clinical findings. It is remarkable that this patient lived 14 days with such extensive damage to the right ventricle. In the reported cases (table 1) and the series of Wang and coworkers,[4f] death resulted within a few days. One is forced to speculate as to the source of the force which propelled enough blood through the lungs to the left ventricle to meet the needs of vital areas for so long. Bakos[3] suggested that it may come from the deep sinospiral muscle of the contiguous left ventricle.

The clinical picture in this and cases 2, 3, and 5 was that of low input-output failure of the left ventricle; that is, fall in blood pressure, collapse of peripheral veins, cold, ashen-gray skin, mental irritability, stupor, anuria, and azotemia. Peripheral congestive failure was not prominent, undoubtedly due to the fact that the factors[1, 29–31] responsible for electrolyte and water retention were operative for too short a period. This supports the views of Starr.[2]

Electrocardographic findings. The tracings in figure 1*B* and in the reported cases (table 1) show that there is nothing distinctive of right ventricular damage. Myers and his group[26] found that the electrocardiogram failed to show any evidence of extension of left ventricular infarction into the right ventricle. In our case, the absence of progress tracings, and complication by the effects of an old posteroseptal infarct and the recent myocardial disturbance incident to the pulmonary emboli, may have been additional factors in reducing the diagnostic value of the electrocardiogram. Some suspicion of the possibility of right myocardial damage may be warranted, however, from the findings of (1) increase in the potential of the small right-sided R waves as the transitional zone was approached; (2) the reciprocal changes in the S-T segments on the right and left side of the precordium, as pointed out by Wolferth and his associates[27] and Dressler and Roessler.[28] A similar effect was reported in case 4 (table 1).

* About 200 Gm. less than the average total weight.

† The lesser physiologic needs of the right ventricle in comparison with the left ventricle, per equivalent muscle mass, are suggested by the following facts: At rest the work output of the right is about one-third that of the left ventricle[17, 18] while the capillary-fiber ratio is about the same.[19] In the clinical entity of congenital anomalous coronary artery[23, 24], when the left coronary artery arises from the pulmonary artery the life span is usually less than six months, compared with an almost normal span when the right is so derived. Further evidence appears in the effects of acute coronary insufficiency secondary to pulmonary embolism where the left ventricle is the usual site of ischemic death.[25]

Summary

1. Search of the literature confirms the clinical impression that massive right ventricular infarction is rare.

2. The pathogenesis of infarction of the right ventricle is briefly discussed.

3. The electrocardiographic diagnosis of right ventricular infarction is difficult because of resemblance of the changes to patterns found in several other cardiac situations. There are no absolute signs of right-sided lesions.

4. Most of the early clinical manifestations produced by damage to the right ventricle are due to low input-output failure of the left ventricle. Signs of peripheral congestive failure may appear but their severity is related to other factors in greater degree than to incompetence of the right ventricle per se. Usually death intervenes too soon to permit severe congestion to appear.

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CLINICAL PROGRESS

Editor: HERRMAN L. BLUMGART, M.D.

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The Pathogenesis of Malignant Hypertension

By G. W. PICKERING, M.A., M.B, F.R.C.P

NO DOCTOR who has had to treat many patients with hypertension can have failed to be exercised by the tragic problem of malignant hypertension. There is now convincing evidence that this syndrome is a simple consequence of the high level of pressure reached in the small arteries and arterioles, and since this hypothesis has a very important therapeutic implication, the evidence on which it is based is assembled here.

In their classic work "Die Brightsche Nierenkrankheit" published in 1914, Volhard and Fahr[1] pointed out that the course of primary or essential hypertension followed one of two paths. In most patients the course was long, and death, when it at length occurred, was due to cardiac failure, cerebral vascular disease or to a disease unrelated to hypertension. The kidneys obtained after death from such patients showed a simple bland sclerosis ("einfache blande Sclerose"), the arteries showing hypertrophy of the elastica, and the arterioles a fatty hyaline change, but apart from the areas of sclerosis the nephrons were well preserved. In some patients, however, mostly younger and with a rather higher diastolic pressure, the onset of a different course was heralded by the appearance of albuminuric retinitis; soon afterwards renal failure appeared and progressed quickly to death in uremia, mostly within the year. In these the kidneys showed not only the changes in the larger and medium sized arteries already described, but intense endarteritis in the small arteries and arterioles, and changes in the renal substance resembling those of nephritis. This kidney they named the "kombinationsform," and believed that it resulted from the superimposition of an exogenous infective nephritis on an endogenous primary vascular hypertension.

In 1919 Fahr[2] described acute arterial lesions which were invariably present in the condition termed by him malignant nephrosclerosis. The lesions were of two types, the first an acute necrosis of the vessel wall with fragmentation of nuclei, deposition of fibrinoid material, and the occasional presence of red cells in the wall; the second, a cellular thickening of the intima without splitting or reduplication of the elastica intima. Fahr pointed out that these lesions were most severe in the kidneys, but that they occurred also, but less constantly, in other organs, notably gut, pancreas and adrenals, but not muscle or skin.

Subsequent work by others, notably Keith, Wagener and Kernohan,[3] Fishberg,[4] and Ellis,[5] has fully confirmed these early clinical and pathologic studies of Volhard and Fahr.[1] But while the classic picture of malignant hypertension is clear enough, further experience has shown that its relation to other forms of hypertension is complex. The hypothesis here presented provides a simple explanation of these complex interrelationships.

HYPOTHESES OF PATHOGENESIS

Volhard and Fahr,[1] as has been mentioned, believed malignant hypertension to be the consequence of the superimposition of nephritis on

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essential hypertension. Fahr continued to believe that the decisive factor in the genesis of malignant hypertension was a toxin causing the acute arterial lesions and usually due to syphilis or polyarticular rheumatism. Volhard,[6] however, changed his ideas after putting forward his hypothesis of pale and red hypertension in 1918. Volhard[7] was struck with the similarity between the clinical features of malignant hypertension and chronic nephritis and with their contrast to those of benign hypertension. In the former, which he called pale hypertension, the arterial pressure, particularly the diastolic, was usually over 130 mm. Hg, the face was pale, the retinal arteries narrow, and the course rapidly fatal. In the latter, the diastolic pressure was usually lower, the retinal arteries were less narrow, the face was often red, and the course relatively stable. He considered that red hypertension was due to the effects of age on a certain genetic constitution, and attributed the hypertension to elastosis of the prearterioles, which became less distensible by the arterial pulse. Pale hypertension was due to active constriction of the small arteries and arterioles by a chemical substance, which he believed to arise from the kidneys as a result of ischemia. He supposed that when in red hypertension the prearterioles contracted sufficiently to the distending pressure to reduce renal blood flow below a certain level, the renal pressor substance was released, and the active vasoconstriction of pale hypertension was added; this change in the mechanism of hypertension was reflected clinically in the change from benign to malignant hypertension. He believed further that the distinctive clinical and pathologic features of malignant hypertension, albuminuric retinitis, acute necrosis, and intimal thickening of the arterioles, were likewise a result of local ischemia consequent on the intense vasoconstriction caused by the circulatory pressor substance. Thus he believed that the development of pale hypertension led to a vicious circle, renal ischemia leading to a release of a renal pressor substance, which led to further renal ischemia with a further intensification of the vasoconstriction.

Volhard's hypothesis is not unlike that put forward here. But his distinction between red and pale hypertension has never been substantiated, for the evidence of his pupils has not been confirmed. Thus Deicke and Hulse's[8] contention that the response to adrenaline was much greater in pale than in red hypertension was not confirmed by Pickering and Kissin.[9] Bohn's[10] claim that a pressor substance could be extracted with alcohol from the blood in pale hypertension but not in red hypertension was not substantiated by the careful experiments of de Wesselow and Griffiths,[11] Aitken and Wilson[12] and Page.[13] Alleged differences in response to the cold pressor test, to overbreathing and to carbon dioxide were not confirmed by us,[9, 14] when care was taken to choose subjects of comparable age groups. In fact, the mechanism of hypertension in chronic nephritis and malignant hypertension is still as little known as it is in benign hypertension.

The hypothesis which is here presented grew out of two chance observations. The first was the observation that the type of retinitis distinctive of malignant hypertension was nearly always associated with a raised cerebrospinal fluid pressure, which in turn seemed to be due to the intensity of the hypertension. The second was the finding that in the rabbit and rat, in which hypertension had been produced by renal artery constriction, the incidence of arteriolar lesions could be attributed to one factor only, the level of pressure reached in the arteries concerned. The hypothesis provides a simple explanation for the incidence of malignant hypertension in hypertensive disease. Further, it was predicted that if the hypothesis were correct, a reduction in arterial pressure should be accompanied by a transformation of the malignant to the benign type of hypertension; this, too, has been confirmed. These successive and cumulative pieces of evidence may now be considered.

The Pathogenesis of Albuminuric Retinitis

It should be clearly recognized that there are two forms of retinitis in hypertension, and that only one of these is characteristic of malignant hypertension. The distinction was first made by Foster Moore,[15] when he showed that there was a type of retinitis, termed by him arterio-

sclerotic retinitis which differed from the albuminuric form in its appearance and its association with a much more favorable prognosis. Albuminuric retinitis, or hypertensive neuroretinopathy,* is a bilateral condition characterized by papilledema, edema of the retina, large ill-defined exudates, hemorrhages and a macular star figure (fig. 1). Arteriosclerotic retinitis (arteriosclerotic retinopathy[16] and "leichte atypische Retinitis"[17]) is usually unilateral, edema of the disc and retina rarely occur; the exudates are small and sharply defined, and a star figure does not occur or consists of discrete dots rather than sheets or lines

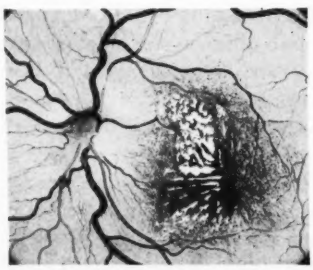

FIG. 1. Albuminuric retinitis; hypertensive neuroretinitis; grade IV retinitis; the retinitis of malignant hypertension. From a male, age 33, whose malignant hypertension was reversed to the benign form by excising a pyelonephritic kidney. Case quoted on page 609.

of exudate (fig. 2); the picture may of course be modified by retinal vein thrombosis. Foster Moore's figures for prognosis suggested, and subsequent experience has shown, that while albuminuric retinitis is the characteristic lesion of malignant hypertension, arteriosclerotic retinitis occurs in the benign form.

That albuminuric retinitis results from the action of a toxin retained or liberated by a diseased kidney has now been abandoned, because it can occur without albuminuria or renal insufficiency. Volhard (1931) suggested that the lesions were due to retinal ischemia, because they occurred only in hypertension, and then only in the type which he called pale hypertension, and because extreme narrowing of the retinal vessels is common in albuminuric retinitis. He further believed that the ischemia was due to vascular spasm and cited in evidence absence of organic changes in the retinal arteries in two cases of albuminuric retinitis examined histologically by Schieck.[18] Because he did not stain his preparations for fat Schieck's findings have been criticized by Verwey,[19] who found lipoid changes in the walls of the retinal arterioles supplying the site of focal changes in albuminuric retinitis. Friedenwald[20] has confirmed these organic arterial changes and has

FIG. 2. Arteriosclerotic retinitis; arteriosclerotic retinopathy; "leichte atypische Retinitis"; the retinitis of benign hypertension. Reproduced from the original paper by Foster Moore, Quart. J. Med. **10:** 29, 1916–17.

stressed the frequency of organic changes in the central artery of the retina in cases where generalized narrowing of the retinal arteries is found. The observations of Mylius[21] and of Wagener,[22] who observed localized constrictions of retinal arteries to come and go, particularly in toxemia of pregnancy, are also cited in favor of retinal artery spasm. For many years I made a practice of looking for such contractions and never saw them, and such was the experience of most of my ophthalmologic colleagues; when a localized constriction was seen, it was visible in the same place at every subsequent examination. Recently, however, Juler,[23] after very careful observation, has seen small constrictions that vary from day to day in toxemia of pregnancy. It is not my purpose to enter further into the con-

* Albuminuric retinitis has been used throughout this paper because it was the term originally in use for the clinical picture to which it refers. Hypertensive neuroretinopathy is probably a better, if a more ugly, expression.

troversy of the extent and frequency of local spastic contraction of retinal arteries, except to record that most of the localized constrictions seen on ophthalmoscopic examination are organic not spastic, and to deplore the term "vasospastic retinitis," which embodies a conception based on speculation rather than evidence. While focal ischemic changes may be responsible for the exudates and hemorrhages seen in albuminuric retinitis, they may be supposed also to be the cause of the exudates and hemorrhages seen in the arteriosclerotic form. Thus Foster Moore showed that in both forms of retinitis the exudates consist of fibrin and of lipoid, both intra- and extracellular.

The distinction between the two forms, and thus between benign and malignant hypertension, is the presence of neuroretinal edema in the albuminuric form and its absence in the arteriosclerotic form, and for this distinction a very different cause is responsible. In 1934 I published a series of observations on the cerebrospinal fluid pressure in hypertension, observations which were made in the hope of explaining hypertensive encephalopathy and headache.[24] It was found that for a given patient, the cerebrospinal fluid pressure measured on separate occasions was remarkably constant in the absence of cerebral vascular accidents, but that it varied from one patient to another. A close correlation was found between the height of the cerebrospinal fluid pressure and the type of retinal lesion found. Thus all of 12 patients with cerebrospinal fluid pressures above 250 mm. H_2O had, or developed subsequently, albuminuric retinitis; of 21 patients with pressures below 250 mm. H_2O, one had albuminuric retinitis, eight had arteriosclerotic retinitis and the remainder no retinal lesions other than arteriosclerosis; three patients provided an intermediate group in which the cerebrospinal fluid pressure was sometimes above, sometimes below the critical level. Shelburne, Blane and O'Hare[25] found papilledema in 19 out of 20 patients with hypertension having cerebrospinal fluid pressures over 200 mm. H_2O, but in only 2 of 30 patients with lower cerebrospinal fluid pressures. Although they made no other distinction between the retinal changes in the two groups, papilledema is usually accepted as the most constant distinguishing feature between albuminuric and arteriosclerotic retinitis.

The association between cerebrospinal fluid pressure and albuminuric retinitis in hypertension is about as close as that between cerebrospinal fluid pressure and papilledema in cerebral tumor. In Ayer's[26] series of 61 patients with cerebral tumor, 42 had cerebrospinal fluid pressures above 250 mm. H_2O and of these 39 had papilledema and three had not; 19 patients had lower cerebrospinal fluid pressures and of these six had papilledema and 13 had not. Thus it would seem that the neuroretinal edema which is characteristic of albuminuric retinitis is due, as in cerebral tumor, to raised intracranial pressure.[24] This explanation was first suggested by Cushing and Bordley[27] in 1908 on the grounds that a raised cerebrospinal fluid pressure was found in many cases of albuminuric retinitis, and that in two cases the retinitis cleared after cerebral decompression. This would, however, seem to be an exceptional result, for in Grant's[28] cases in which decompression was performed for suspected cerebral tumor, both retinitis and raised cerebrospinal fluid pressure persisted after operation.

An investigation into the factors that might be responsible for the raised intracranial pressure in albuminuric retinitis detected only two, namely, the degree of anemia, and the degree of hypertension.[24] The relationship between cerebrospinal fluid pressure and diastolic arterial pressure is shown in figure 3 and is statistically significant. Brain's[29] observations on cerebral tumor showed no relationship between the degree of raised intracranial pressure and the arterial pressure, and it would seem, therefore, that in some way the raised cerebrospinal fluid pressure is a consequence of a sufficiently severe hypertension. Volhard (personal communication) suggested that this relationship was due to ischemic cerebral damage, but the protein concentrations in the cerebrospinal fluid were very little different in the two series. It would seem more likely that the level of arterial pressure is in part transmitted to the choroid plexus, owing to the poor contractility of the cerebral arteries. Curiously enough, when raised cerebrospinal fluid pressure is a

consequence of raised venous pressure, as it may be in cardiac failure or superior caval obstruction, papilledema does not usually occur, perhaps because in this instance intraocular and intracranial pressure may be equally affected by the same cause.[30]

In its full form the hypothesis of the pathogenesis of the retinal lesions is thus as follows. Focal lesions such as hemorrhages and exudates are probably due to focal vascular obstruction, either arterial, due to organic or spastic occlusion and more commonly the former, or venous; for, as Moore[31] showed, retinal venous occlusion is not uncommon in hypertension and is characterized by exudates and hemorrhage in the affected territory. These focal lesions are common to the albuminuric and the arteriosclerotic form. But the distinguishing feature of albuminuric retinitis is the presence of widespread neuroretinal edema and this is a consequence of the level of intracranial pressure and indirectly of the severity of the hypertension.

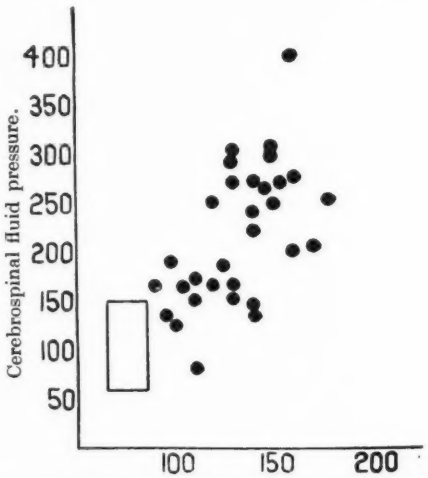

FIG. 3. The relationship between cerebrospinal fluid pressure and diastolic arterial pressure in hypertension (Pickering, Clin. Sc. 1: 397, 1933–34).

This explanation of arteriosclerotic and albuminuric retinitis is in conformity with the fact that while most cases belong clearly to one or other type, it is not uncommon to see intermediate forms or to see one develop out of the other. For instance, small, hard-edged exudates may be the sole lesion until bilateral papilledema marks the transition to the malignant phase.[24] Again, when the arterial pressure is reduced, and the malignant converted to the benign phase, papilledema goes first, and the exudates shrink and become more sharply defined.[32]

The Pathogenesis of Acute Arteriolar Necroses

The experimental production of acute arteriolar necroses in hypertension was first described by Goldblatt in 1938.[33] He observed these lesions in dogs in which the renal arteries had been tightly constricted, leading to gross hypertension and renal insufficiency. The lesions resembled those found in malignant hypertension in man, both in their appearance and in their distribution amongst the tissues of the body, except for their absence in the kidneys, the arteries to which had been clamped. Goldblatt considered that two factors participated in producing these lesions, a gross rise in intravascular pressure, and renal insufficiency. Shortly afterwards, and independently, similar lesions were described in the rabbit.[34] As in malignant hypertension in man the lesions were of two kinds, namely, acute fibrinoid necrosis of the media and intima or both, with or without a cellular reaction, and cellular intimal thickening which, we suggested, represented an organization of an earlier fibrinoid necrosis. These lesions were most frequent and severe in the intestine; they were present in occasional vessels in the stomach, suprarenal, liver, myocardium and eye. No lesions were found in skin or striated muscle; nor were lesions found in the kidney of which the renal artery had been constricted, except in one rabbit, in which both renal arteries had been constricted, and in which a few lesions were found close to the areas of infarction in the smaller kidney. These acute arterial lesions were only found in rabbits in which the arterial pressure had risen above a certain point, and we therefore attributed them to the gross rise in intra-arterial pressure, attributing the sparing of the kidney to the protection afforded by the constricting clamp on the renal artery. It was not possible to put

this hypothesis to the test of a crucial experiment in the rabbit, because in this animal as in the dog, the grosser degrees of hypertension necessary to produce the lesion can only be produced by constricting both renal arteries, or by constricting one after the other kidney has been removed. The crucial experiment was, however, carried out in the rat by Wilson and Byrom.[35, 36] These authors showed that in the rat gross persistent hypertension can be produced by constricting one renal artery while the other kidney is intact. In such animals acute arterial lesions identical with those of malignant hypertension were found in the intestine, pancreas, suprarenal and heart and in the kidney, the artery to which was not clamped. The lesions were absent from the kidney whose artery was clamped, at least in the early stages, although later this kidney also showed similar but less extensive lesions. They showed, in beautiful illustrations, that the lesions in the unclamped kidney of the rat were identical in all stages with those found in the human kidney in malignant hypertension. Since the blood urea was normal in many of their animals they concluded that hypertension alone was the causative factor. Unlike Wilson and Pickering in the rabbit, they did not find a relation between the intensity of hypertension and the presence or absence of lesions, but whereas in the rabbit the arterial pressure was measured without anesthesia, in the rat the pressure was measured under anesthesia, which itself may influence the arterial pressure.

Wilson and Byrom went further. They showed that after acute arterial lesions had developed in the untouched kidney, excision of the clamped kidney was not followed by a return of arterial pressure to normal. They showed that the extent to which hypertension persisted after removal of the kidney whose renal artery had been clamped was related to the intensity of the lesions in the other kidney. They were therefore led to the conception of a vicious circle in Bright's disease, as Volhard had suggested on clinical grounds, in which hypertension produces arteriolar lesions in the kidney, which in turn produce an intensification of hypertension. The role of the kidney in the mechanism of chronic hypertension is still so obscure that the conception of a vicious circle is still based on rather slender evidence and is no part of the thesis presented here.

Goldblatt's objection to the experiments of Byrom and Wilson, namely, that the acute arterial lesions were due to spontaneous pyelonephritis, has been effectively answered by Byrom and Dodson,[37] who produced further evidence that a rise of intravascular pressure can itself produce the lesions. Injecting 2 cc. of warm saline through a wide bore needle into the aorta 10 or 15 times in anesthetized rats, they found acute arteriolar necroses in the kidney, when the animals were killed three days later. When one kidney was protected during the injections by traction on a ligature looped around its renal artery, lesions were absent in that kidney though present in the other which had been subjected to the full pressure rise. The degree to which intra-aortic pressure was raised was at least 80 to 90 mm. Hg. These experiments lend support to the idea, put forward by Schurmann and MacMahon[38] that acute necrosis is due to a breach of the endothelial lining which, if mild, would allow the escape of plasma into the wall, and if severe would permit the passage of red and white cells also.

While these experiments would seem to provide a convincing explanation of the acute arterial lesions of malignant hypertension, the question is so important that other possibilities must be considered. Volhard thought the lesions were due to vascular spasm producing local ischemia. Arteriolar necrosis has been found in the edge of infarcts by Russel[39] and by Byrom[40] in the kidney in which intense vasoconstriction has been induced by intravenous injection of vasopressin. It is not easy to dismiss with finality the idea that local ischemia may cause these lesions in man, where Goldring, Chasis, Ranges and Smith[41] have shown the renal blood flow is diminished per unit of functioning renal substance; for while it may be stated that the degree of reduction of blood flow is insufficient, it is a possible, if rather tenuous, argument that the over-all picture obscures local decreases that are much more extreme. The evidence already detailed

makes such an explanation of acute arterial lesions in hypertension quite unnecessary. Moreover, ischemia probably plays no part in the genesis of these lesions in experimental hypertension, since the kidney with clamped artery, far from being most affected, is actually spared.*

A very different explanation has been put forward by Winternitz and his colleagues.[42] They found that, in the dog, bilateral nephrectomy killed the animal without hypertension or vascular lesions. Bilateral ligature of the renal arteries or of the ureters produced hypertension and necrosis of muscle "including heart muscle, smooth muscle of blood vessel walls, hollow viscera and diaphragmatic muscle." Thinking that a renal substance might be responsible for these tissue lesions, they showed that injection of stored saline extracts of necrotic and fresh dog's kidney produced a profound fall followed by a prolonged rise of pressure in nephrectomized dogs, the same lesions being found at post-mortem examination as after ureteric or renal artery ligation. Working with hog renin, they were unable to separate the pressor fraction from that producing the tissue injury. Experiments differing in detail but with a similar import were published by Leiter and Eichelberger.[43] They injected hog renin into dogs which developed a foreign protein reaction. In 15 dogs with experimental renal lesions death occurred within a few days of the injection, and in 12 of these the arterioles showed hyaline degeneration and fibrinoid necrosis with leukocyte emigration and hemorrhage; in four of these dogs there was not sufficient renal damage nor severe enough hypertension to account for the lesions. So far as our present problem is concerned these experiments are open to two very serious criticisms. In the first place, hog renin is known to be antigenic in the dog,[44] and Rich and Gregory[45] have shown that the injection of foreign protein produces widespread arterial lesions, in which fibrinoid necrosis is a prominent constituent, though the whole picture is akin to that of periarteritis nodosa. In the second place, none of these extracts were prepared under aseptic precautions, nor were they sterilized before use. It is a well-known trap in the case of the dog, that the tissues contain *Clostridium welchii* even when excised aseptically.[46, 47] Experiments from this laboratory have shown that intravenous infusions of rabbit renin into rabbits produce death with widespread hemorrhage unless extreme care is taken to sterilize the extracts and to work under strict aseptic conditions. With strict asepsis, infusions of rabbit renin into rabbits produces hypertension that is maintained for the duration of the infusion (up to 18 days), the intensity of the hypertension varying with the logarithm of the dose of renin infused.[48] In such animals acute arteriolar necroses were not found, except mildly in two animals in which the level of arterial pressure had been previously raised by subtotal nephrectomy.[49] Surveying these animals together with those earlier reported in which hypertension had been produced by renal artery constriction it was clear that the factor producing arterial necrosis was the level of arterial pressure actually attained.

* It is to be noted that after clamping the renal artery to one kidney, the other having been removed, the renal blood flow at first falls and later rises to its original level. In experiments such as those of Wilson and Byrom in which one renal artery is clamped, the other kidney being intact, it is assumed that blood flow falls through the clamped kidney, but this has not actually been shown.

The Natural History of Malignant Hypertension

A test of the validity of a hypothesis is its usefulness in interpreting established data. The hypothesis now under consideration provides a simple explanation for many of the features of the natural history of malignant hypertension that have previously been obscure.

The syndrome of malignant hypertension has three chief components: albuminuric retinitis, rapidly progressing renal failure, and the presence after death of arteriolar necrosis. While albuminuric retinitis is the rule it is not indispensable. Thus Goldring and Chasis[50] state that in their 68 patients in whom the diagnosis of malignant hypertension was established at necropsy, papilledema was absent in 16, or 23 per cent. In two out of five patients in whom acute necroses were found in a surgically excised pyelopephritic kidney, exudates similar

to those of albuminuric retinitis were present in the fundus but no papilledema; conversely in one patient with typical albuminuric retinitis no acute necroses were found in the excised kidney or in either excised adrenal.[52] Derow and Altschule[51] failed to find arteriolar necroses in the kidneys of some of their patients with malignant hypertension and in others found only few, but necroses were found in the arterioles of other organs. Keith and Wagener[53] and Ellis[5] have described cases in which albuminuric retinitis was present during life and arteriolar necroses after death and in which renal function and renal anatomy were essentially normal at death from cardiac or cerebral cause. The variability in these findings becomes at once comprehensible on the present hypothesis, for albuminuric retinitis and arteriolar necroses are separately caused by the sustained rise of arterial pressure above a certain level; and it would not be in conformity with other biologic phenomena if these two responses had precisely the same threshold to a given stimulus in all individuals. Moreover, if we are right in believing that productive endarteritis may sometimes be due to the organization and healing of arteriolar necroses, gross arteriolar disease can be present in the absence of necroses themselves. Since rapid renal failure is the effect of acute arteriolar lesions developing and progressing in the kidneys, since these lesions are not confined to the kidney and since there may be other consequences of gross hypertension such as cardiac failure, death may occur before renal function has significantly declined.

Even if we employ the strictest criteria and demand for its diagnosis all three phenomena, albuminuric retinitis, progressive renal failure and the presence after death of arteriolar necroses, we find that the malignant hypertension group is not homogeneous. Thus all three phenomena are found in certain cases of glomerulonephritis either in the acute, the subacute or the chronic stages. It was this above all that led to the delayed recognition of malignant hypertension and still makes its diagnosis difficult. Thus it is often difficult to be sure whether a patient is suffering from the malignant termination of essential hypertension or that of nephritis. When a patient appears with no history of acute nephritis, with albuminuric retinitis and normal urea clearance or capacity to concentrate urea, the malignant phase of essential hypertension can be diagnosed with confidence. When he presents a past history of acute nephritis, albuminuric retinitis and renal failure, the terminal phase of nephritis is probable. But when, as is common, the patient has no unequivocal history of acute nephritis and is first seen with albuminuric retinitis, gross hypertension and renal failure, it is impossible during life, and often difficult after death, to distinguish between nephritis and the malignant phase of essential hypertension. In the older British writings malignant hypertension was referred to as "chronic interstitial nephritis," and in Russel's[39] classification of Bright's disease as "nephritis repens, type IV." Volhard and Fahr's[1] recognition of the entity of malignant hypertension was a masterly example of clinical insight, but even they were so impressed by the similarity of the histologic features that they at first regarded the condition as nephritis grafted on to essential hypertension, naming it the "Kombinationsform." It was only later with further experience and reflection that they severally recognized its distinctive features. Rapid renal failure in glomerulonephritis can, of course, occur as a result of the nephritic process itself. But hypertension is the rule in nephritis and, if sufficiently severe and acute, it can cause albuminuric retinitis and arteriolar necroses, the presence of which were demonstrated in nephritis by Klemperer and Otani,[54] Fishberg,[4] Derow and Altschule.[51] These acute arteriolar lesions located in the kidney add to the rate and extent of renal destruction, as Wilson and Byrom[35, 36] pointed out and illustrated so beautifully.

Nephritis is, however, not the only disease that may confuse the picture. In 1929 Ask-Upmark[55] described six cases of malignant hypertension in adolescents in which was found a peculiar renal lesion characterized by unilateral hypoplasia, and an enlarged and deformed renal pelvis having one or more recesses ending blindly near the surface of the kidney. It is probable from the description of these cases that the kidney was the seat of pyelonephritis

the relation of which to hypertension and to its malignant phase was first clearly presented by Longcope in 1937.[56] Since then very many cases of pyelonephritis complicated by malignant hypertension have been described. In fact, in Weiss and Parker's[57] experience at the Boston City Hospital pyelonephritis accounted for some 15 to 20 per cent of patients with malignant hypertension.

In 1934 MacMahon, Close and Hass[58] described two cases of Cushing's syndrome in which the post-mortem findings were those of malignant hypertension. In 1935 MacMahon and Pratt,[59] reviewing malignant nephrosclerosis, concluded that it was not merely a progression of benign sclerosis, but a distinct and separate disease that might exist alone or complicate benign sclerosis. They considered that the etiology of benign and malignant hypertension had much in common since they might both occur in lead poisoning, pituitary basophilism, and toxemias of pregnancy. In the same year, Derow and Altschule[51] described a series of cases, and, after reviewing previous writings, concluded that malignant hypertension is "a syndrome which may occur (a) with no evidence of previously existing hypertension, (b) as the end stage of essential hypertension, with, or without uremia and (c) as the end stage of a miscellaneous group of conditions characterized by hypertension secondary to acute, subacute or chronic glomerular nephritis, pyelonephritis, adrenal tumor, pituitary basophilism, periarteritis nodosa, hyperemesis gravidarum, chronic lead poisoning, et cetera." Derow and Altschule[60] repeated their suggestion in 1941, and gave a comprehensive review of the relevant material. They stated that "The mechanism by which the benign course of primary or secondary hypertension is suddenly and dramatically transformed into the rapid, progressive, downhill course of the syndrome of malignant hypertension is not understood. Attempts to incriminate infectious toxins, mental stress or other factors have been inconclusive." In 1942, influenced by the considerations earlier presented in this paper, and ignorant of Derow and Altschule's views, I wrote[30]: "Thus we see on the one hand that the causal lesion is not always the same in malignant hypertension, and on the other that a given kind of lesion may be accompanied by a hypertension that follows either the benign or the malignant course. These features are readily explained on the view that the benign and malignant courses of hypertension are merely expressive of the severity of the hypertensive process, irrespective of the lesion which alternately determines it".

We still know very little of the mechanism that produces hypertension, though there are grounds for believing that it may differ in different diseases. In pheochromocytoma, paroxysmal hypertension is almost certainly due to discharge of adrenaline and noradrenaline into the blood stream; in this disease I have seen albuminuric retinitis, as have others, but know of no recorded instance of arteriolar necroses. In some cases of unilateral pyelonephritis, hypertension is renal in origin and is cured by excising the kidney; albuminuric retinitis, arteriolar necroses and rapid renal failure are well known in such cases, but the precise mechanism by which the kidney raises blood pressure is still obscure. In nephritis the occurrence of malignant hypertension has been discussed. I have seen albuminuric retinitis, rapid renal failure and the occurrence of arteriolar necroses in polycystic kidney with gross hypertension. Other renal abnormalities are discussed by Derow and Altschule,[60] but in none of these is it known with certainty whether the hypertension arises from a renal cause. The cause of hypertension in toxemia of pregnancy, Cushing's syndrome and in essential hypertension is also still obscure. Since the mechanism causing hypertension is still unknown in these diseases, it is not surprising that the factors which lead to the accentuation of hypertension and thus, *ex hypothesi*, to the transition from the benign to the malignant form, are also quite unknown. The question has been reviewed elsewhere.[61] Finally, in coarctation of the aorta, hypertension is abolished by excision of the constriction, though by what process is not known. Coarctation of the aorta is the only form of hypertension yet recognized in which I have never seen albuminuric retinitis, progressive renal failure or arteriolar necroses, nor am I acquainted with a description of them.

In all these forms of hypertension, then, except coarctation of the aorta, the course of hypertension may be benign throughout, or at first benign and then malignant, and the contention here is that the nature of the course is determined by the level of the arterial pressure. This hypothesis can not be fully investigated, chiefly because of the large and unknown variations in arterial pressure during the 24 hours, and the possibility, from Byrom and Dodson's work,[37] that arteriolar necroses are caused by very high pressure operating for quite short periods. But what is known of the arterial pressure seems to be in conformity with the hypothesis. Thus all who have studied malignant hypertension from the time of Volhard have been impressed with the high level of diastolic arterial pressure (usually over 140 mm. Hg). In Woods and Peet's series of patients who had sympathectomy for hypertension, the average pressures were 191/115, 217/131, 225/134 and 227/148, respectively, in groups 1, 2, 3 and 4 before operation, group 4 being malignant hypertension.[62] Similarly, in Bechgaard and Hammerstrom's series[63, 64] the incidence of high systolic and diastolic pressures was greatest in the malignant group. But while it is true in general that the arterial pressure is higher in malignant than in benign hypertension, there are individual exceptions. On the one hand, the diastolic arterial pressure may be persistently above 140 mm. Hg for many years without albuminuric retinitis or renal impairment developing. On the other, albuminuric retinitis and arteriolar necroses may develop in patients who have persistently had lower pressures, especially in those whose hypertension is of recent origin. There are several possible explanations for these anomalies. The most probable is that these anomalies may represent no more than the usual variations in susceptibility of a heterogeneous population to a stimulus of given intensity. Other possible, but quite unproved, causes are that the arterioles may be protected by organic arterial changes developing proximally in long continued hypertension, or conversely, that the arterioles may be unduly exposed to the arterial pressure by vasodilatation induced by anemia, which often accompanies the more acute hypertension. These are the kind of anomalies met with in all biologic work and their occurrence does not diminish the importance of the statement that the arterial pressure is in general higher in malignant than in benign hypertension.

In hospital practice it is not common to see the transition from the benign to the malignant type of hypertension, since most cases of malignant hypertension are seen for the first time with albuminuric retinitis. But I have followed five cases over several years before the development of malignant hypertension and through the malignant phase to its termination. Three of these cases were of essential hypertension and two of pyelonephritis. In all five the arterial pressure was considerably lower when first seen than it was at the onset and throughout the course of the malignant phase.

One further feature of the natural history of the disease requires notice. Since, *ex hypothesi*, the benign and malignant courses are mere consequences of the degree of hypertension, it would be expected that the difference between them is not absolute, and that in certain patients where the pressure is close to the threshold level, characteristic features of malignant hypertension may come and go. This is most easily seen in the fundus oculi, where it is not uncommon to see exudates, that are too large and too ill-defined for those typical of the arteriosclerotic form, to come and go before the accession of bilateral papilledema completes the picture of albuminuric retinitis. That the retinal picture of malignant hypertension may on occasion spontaneously revert to that of the benign type has been pointed out by Keith and Wagener.[53]

The Treatment of Malignant Hypertension

A further test of the validity of a hypothesis is its ability to predict new data.

The hypothesis here presented enabled the prediction to be made that if the arterial pressure could be reduced sufficiently, the malignant course of hypertension would be reverted to the benign type. For many years there has been little doubt that this in fact is so. When arterial pressure is reduced by sympathectomy, by anterior spinal root section, by pyrogens, or

by salt free diet, albuminuric retinitis disappears, and the experience of Smithwick[65] and Hammerstrom and Bechgaard[63, 61] suggest that life is prolonged, though it is to be noted that none of their series fulfills the conditions as to controls rightly demanded by Hill.[66] However, no cases of reversion had been published with histologic proof of malignant hypertension until we recently described three.[67] The cases were of pyelonephritis, unilateral in one, bilateral in two; all had the full picture of albuminuric retinitis with bilateral papilledema, large ill-defined exudates and star figure; and in all arteriolar necroses were found in kidney and suprarenal at operation. In a male aged 33 hypertension was reduced from an average 230/160 to 150/110 over a period of six years by removal of the affected kidney and the adrenal, splanchnic nerves and lumbar ganglia on the same side. Retinitis cleared quickly and renal function is normal six years later. In a girl aged 13, removal of the more affected kidney produced a slight fall, and excision of the whole of one and three-fourths of the other adrenal produced a further fall of arterial pressure not fully maintained. Six years later she has still some hypertension, gross organic changes in the retinal arteries and normal renal function. In the third case, a girl aged 11, bilateral splanchnic section and excision of seven-eighths of the adrenals produced a fall in pressure from 250/175 to 150/110 which has been maintained since. Five years later she has mild hypertension, normal fundi and normal renal function. Survival for six years with no retinitis or urea retention at the end seems to us clear evidence that the malignant course had been altered to the benign by measures which had only this in common, that they produced a significant and prolonged reduction in arterial pressure.

Thus it may be stated with some confidence that in any patient with hypertension due to any cause and at any age, the appearance of albuminuric retinitis makes it imperative that measures should be taken at once to reduce arterial pressure and keep it down, if the patient's life is to be spared. If not, the arteriolar necroses consequent on severe hypertension will kill him.

Summary and Some Conclusions

The response of the body to raised arterial pressure includes cardiac hypertrophy and medial hypertrophy of the arteries. There is also some evidence that affections of the largest and moderate sized arteries, atheroma and elastosis, are more widespread and severe when the arterial pressure is raised for long periods. Provided the arterial pressure does not pass a certain critical level, these are the major consequences of hypertension, and on the whole they present a rather stable picture, except for the thrombotic occlusion of atheromatous coronary or cerebral arteries, and the accession of cardiac failure, which is not necessarily ischemic in origin. This relatively stable picture in which the patient's condition remains unchanged often for many years is termed the benign phase of hypertension, and is most commonly seen in those types of hypertension in which the causal lesion is itself stable, particularly in essential hypertension and coarctation of the aorta, to a less extent in chronic pyelonephritis, polycystic kidney and Cushing's syndrome; it may also occur in chronic nephritis in which, however, the clinical course is often dominated by the nephritis lesion itself.*

Should, however, the pressure rise above a certain critical value, which varies from one patient to another about an average of 140 mm. Hg diastolic, then albuminuric retinitis is seen, and acute necroses occur in the arterioles of many organs, particularly of kidney, intestine, abdominal viscera, heart and brain. These acute necroses expand the wall at the expense of the lumen and seriously interfere with the blood flow to territories they supply. This is particularly important in the kidney and results in the appearance of albumin and red cells in the urine and progressive decline of renal function terminating in uremia. The weakening of the arterial wall consequent on its necrosis is prob-

* Volhard[1, 6, 7] and Wilson and Byrom[36] have drawn attention to this type of case of which I have seen many examples. The patient has had acute nephritis, followed by persistent albuminuria, and has a moderate hypertension with albumen and usually a small excess of red cells and casts in the urine and normal or slightly impaired renal function; the condition remains unchanged for years.

ably the chief cause of cerebral hemorrhage that may also terminate the malignant phase. The great load imposed on the heart by the high pressure of malignant hypertension may also be held responsible for left ventricular failure, the third mode of death in this condition. The course of hypertension may change from benign to malignant in any disease in which the pressure rises above the critical level. Because essential hypertension is by far the commonest type, this provides the bulk of malignant hypertension, followed by chronic pyelonephritis, acute, subacute and chronic nephritis, polycystic kidneys, periarteritis nodosa, Cushing's syndrome, pregnancy toxemia, and possibly pheochromocytoma, in roughly that order. In coarctation it would seem that hypertension is never gross enough to produce the malignant phase. Once albuminuric retinitis has appeared or the malignant phase has been diagnosed, a persistent and considerable reduction of the arterial pressure becomes the single and urgent aim of therapeutics.

There has been in the past much argument as to when the term malignant hypertension should be used. In the light of the considerations discussed here much of this argument would seem specious and irrelevant. The malignant phase has a reasonably precise implication for both prognosis and therapeutics and can complicate nearly any type of hypertension. It would therefore seem proper to speak as Fishberg[4] does of the malignant phase of hypertension, but also to relate it to the underlying disease whether this be essential hypertension, pyelonephritis, pregnancy toxemia, nephritis, polycystic kidney or the like. In this way, the name given by the doctor in his diagnosis is not only reasonably full and accurate, but prepares the way for the correct management of the case.

Summary

Whether hypertension follows the benign or the malignant course depends chiefly on the severity of the hypertension. Malignant hypertension may develop in hypertension due to any cause, provided it is sufficiently severe. The evidence for this hypothesis is as follows:

1. The characteristic finding in malignant hypertension during life is albuminuric retinitis (hypertensive neuroretinopathy) which differs from the retinitis of benign hypertension (arteriosclerotic retinitis) in the presence of neuroretinal edema. This neuroretinal edema is due to raised intracranial pressure, which in turn seems to be a consequence of the high level of diastolic arterial pressure.

2. The characteristic finding in malignant hypertension after death is acute arteriolar necrosis, the occurrence of which in the kidneys is chiefly responsible for the rapid renal failure which is so often the cause of death. Evidence from animal experiments suggest that the chief factor determining these arteriolar necroses is the high level of arterial pressure.

3. Albuminuric retinitis, rapid renal failure and acute arteriolar necroses may occur in essential hypertension, acute and chronic nephritis, pyelonephritis, polycystic kidney, Cushing's syndrome and toxemia of pregnancy; these conditions may terminate therefore in the malignant phase. Alternatively, the hypertension may be stable, and, provided the underlying disease is stationary, the patient's condition may remain unchanged for many years; the hypertension may thus have the characteristics of the benign type.

4. In patients whose hypertension changes from the benign to the malignant phase, it is usual to find that the arterial pressure is higher in the malignant than in the benign phase.

5. It has been proved that hypertension can be reversed from the malignant to the benign phase by measures which reduce the arterial pressure.

It would therefore seem correct to speak of the malignant phase of hypertension and to relate this to the underlying malady whether this be essential hypertension, pyelonephritis or the like. The diagnosis of the malignant phase of hypertension carries a single and urgent therapeutic implication, namely, the prompt and persistent lowering of arterial pressure.

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ABSTRACTS

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BACTERIAL ENDOCARDITIS

Wallach, R., and Pomerantz, N.: Combined Antibiotic Therapy. Arch. Int. Med. **88:** 840 (Dec.), 1951.

A report is made of a case of subacute bacterial endocarditis reinfected with a diphtheroid and successfully treated with a combination of penicillin and bacitracin given parenterally. In vitro sensitivity tests, using combinations of penicillin and streptomycin and of penicillin and bacitracin, showed synergism against the organisms tested. A suggestion is made that parenteral treatment with bacitracin might be of value when bacitracin is used in lower dosage in combination with penicillin for its enhancing effect.

BERNSTEIN

Wolfe, E. I., and Henderson, F. W.: Mycotic Endocarditis. J.A.M.A. **147:** 1344 (Dec. 1), 1951.

Only six cases of mycotic endocarditis had been reported prior to the publication of this article. These six cases had occurred in addicts who used drugs intravenously. The present case in which the etiologic agent was *Candida krusei* occurred in a 57 year old woman who was diabetic and who gave herself daily injections of insulin. The patient had a mild fungus infection on the external genitalia which was not identified by smear or culture, but the authors feel the source of contagion may have been in this area. Numerous therapeutic trials of antibiotics and sulfonamides failed and she died three months after admission to the hospital. The antibiotics she received included massive doses of penicillin, aureomycin and dihydrostreptomycin. She was given gantrisin®, sulfamerizine, and sulfadiazine at varying intervals during her period of therapy.

Postmortem findings confirmed the presence of disseminated moniliasis. The case illustrates the necessity for more careful sterilization technic when parenteral medication is being administered by untrained personnel.

KITCHELL

Heatherman, M. E., and Clapper, W. E.: The Relation between Resistance to Chemotherapeutic Agents and Other Biochemical Properties of Some Viridans Streptococci and Enterococci. J. Lab. & Clin. Med. **38:** 881 (Dec.), 1951.

The biochemical tests which correlated best for differentiating *Streptococcus viridans* from the enterococci were the reduction of 0.1 per cent methylene blue milk, the growth on 40 per cent bile agar, the growth in 6.5 per cent sodium chloride broth, growth in broth at 45 C., and in sulfathiazole broth (10 mg. per milliliter) and in penicillin broth (2 units per milliliter).

The enterococci are more resistant in vitro than the viridans streptococci to sulfathiazole, penicillin, streptomycin, aureomycin and bacitracin. They are more susceptible to low concentrations of aureomycin and bacitracin.

Cross-resistance was found in most of the trained resistant strains to all of the agents. All the trained sulfathiazole-resistant strains were considerably more resistant to penicillin, and all of the trained penicillin-resistant strains were highly resistant to sulfathiazole. There was less cross-resistance to streptomycin. Streptomycin-resistant trained strains showed less resistance to the other agents.

The acquisition of a high resistance to sulfathiazole, whether by training in sulfathiazole or in other agents, was accompanied by a change of properties

to those resembling an enterococcus. Only one of six streptomycin-resistant variants acquired these properties.

MINTZ

BLOOD COAGULATION

Crane, C.: The Use of Heparin-Gelatin-Dextrose in Venous Thrombosis and Pulmonary Embolism. New England J. Med. **245:** 926 (Dec. 13), 1951.

The author reports the results in 100 surgical patients with thromboembolic disease treated with heparin-gelatin-dextrose as the sole anticoagulant agent. Vasoconstrictors were used with the anticoagulant in 94 per cent of the patients. Eighty-nine patients had deep venous thromboses with accompanying pulmonary embolism in 20 cases. Eleven patients had pulmonary emboli without demonstrable venous thrombosis.

Failure of therapy was considered to have occurred in seven cases inasmuch as four suffered further pulmonary emboli and three had early recurrence of deep venous thrombosis after treatment. Nausea, palpitation, paresthesias, hot flashes, blurring of vision and local abscesses were very occasional complications of treatment.

The conclusion is that the heparin-gelatin-dextrose mixture given in conservative doses is a simple, convenient and effective anticoagulant for use in selected cases. It is said to be contraindicated in patients for whom lumbar sympathetic block or surgery is to be performed for iliofemoral venous thrombosis with arterial spasm, or in thromboembolic disease occurring in patients recovering from recent urologic, orthopedic, neurosurgical or thoracic surgical procedures.

ROSENBAUM

Van Itallie, T. B., Geyer, R. P., and Stare, F. J.: Vitamin K_1 Emulsions in Bishydroxycoumarin Emergencies. J.A.M.A. **147:** 1652 (Dec. 22), 1951.

Various forms of vitamin K have been used to reverse bishydroxycoumarin-induced hypoprothrombinemia. The relative ineffectiveness of most of these preparations is indicated by the fact that responses to them are usually reported at 24-hour intervals. A potent, rapidly acting vitamin K preparation for the treatment of such hypoprothrombinemia in the dog has been reported. This is a 5 per cent emulsion of vitamin K_1 for intravenous administration.

The authors report the effect of this on two cases and find it extremely effective in bringing about a prompt decrease in hypocoagulability of the blood. These are compared with a third case in which a commonly available water-soluble vitamin K preparation was used. This latter was much slower in action than the emulsion of vitamin K_1 used in the first two patients.

KITCHELL

Hauch, E. W., and Barker, N. W.: Experiences with Heparin: Comparative Effects of Intravenous and Subcutaneous Administration in the Same Individuals. J. Lab. & Clin. Med. **38:** 550 (Oct.), 1951.

A study was made in 20 human subjects of the effects of heparin given intravenously in 50 mg. doses and heparin given subcutaneously in a slowly absorbed medium in 200 mg., 400 mg. and 600 mg. doses. The authors were aware of the fact that the series of cases studied was small and that the coagulation time of whole venous blood is subject to errors and inconsistencies.

It appeared from this study that the degree of prolongation of the coagulation time following intravenously administered heparin cannot be used to predict the degree and duration of effect of a fixed dose of heparin given subcutaneously. Single doses of 400 mg. or 600 mg. of heparin given subcutaneously in a slowly absorbed medium produced an adequate prolongation of the coagulation time usually for less than 24 hours. In several instances, the prolongation of the coagulation time was longer than 24 hours. The unpredictable variability of degree and duration of effect of the heparin administered subcutaneously in a slowly absorbed medium indicates that if heparin is given by this method, an adequate, continuous and not excessive antithrombotic effect can be achieved only by individualization of dosage for each patient on the basis of frequent coagulation tests during the period of heparinization.

MINTZ

Owren, P. A., and Aas, K.: The Control Of Dicumarol Therapy and the Quantitative Determination of Prothrombin and Proconvertin. Scandinavian J. Clin. & Lab. Invest. **3:** 201 (July), 1951.

The authors have studied both the prothrombin and proconvertin (P and P) method and the specific determinations of prothrombin and proconvertin concurrently. The latter methods have not proved superior to the prothrombin and proconvertin method as a guide for the administration of dicumarol. For practical reasons, therefore, the prothrombin and proconvertin method is preferred as the routine clinical method, the estimation being done in one step. On the other hand, the specific determination of prothrombin and proconvertin is an excellent research tool in a variety of other clinical conditions.

The authors believe that the determination only of prothrombin as a guide to dicumarol therapy is unsuitable. During the first phase of treatment the proconvertin concentration very often decreases more rapidly than that of prothrombin. A dosage based only on the prothrombin determination, therefore, may in some cases very likely result in overdosage with risk of bleeding. During treatment over an extended period it has also been observed

that proconvertin may drop to a dangerously low level with the risk of hemorrhage, while the prothrombin concentration is still in the so-called therapeutic range. In most instances, however, the concentrations of prothrombin and proconvertin differ very little.

BERNSTEIN

CONGENITAL ANOMALIES

Goldzieher, J. W., McMahon, H. E., and Goldzieher, M. A.: Coarctation of the Abdominal Aorta Simulating Pheochromocytoma. Arch. Int. Med. **88:** 835 (Dec.), 1951.

A 45 year old woman, presenting symptoms which resembled the clinical picture of pheochromocytoma, but showing negative reactions to tests with adrenolytic drugs, underwent surgical exploration and was found to have a coarctation of the abdominal aorta.

Location of the coarctation near the origin of the renal arteries would suggest strongly that some disturbance of renal dynamics was involved in the hypertension. However, hypertension associated with natural or artificial renal artery lesions is not of the paroxysmal type seen in this case. Unfortunately, it was not possible to carry out studies of renal function to elucidate this factor.

No satisfactory explanation can be offered for intermittent hypertension in the presence of a static narrowing of the aortic trunk. It is, of course, entirely conceivable that the anatomic lesion and the clinical picture of paroxysmal hypertension were entirely coincidental. Even in these circumstances, however, the pathogenesis of the paroxysmal hypertension is no less obscure.

BERNSTEIN

Rogers, H. M.: Disturbances of Cardiac Rhythm and Conduction in Congenital Cardiac Disease: Report of Five Cases. Ann. Int. Med. **35:** 1276 (Dec.), 1951.

Five cases of disturbance of cardiac rhythm or conduction bearing some relationship to congenital heart disease are reviewed. In three cases (two cases of supraventricular tachycardia and one of complete heart block), the cardiac disturbance of rhythm or conduction proved to be acquired in the presence of the following respective congenital cardiac anomalies: (1) probable Eisenmenger's Complex, (2) ventricular septal defect, (3) infantile coarctation of the aorta. In two cases with arrhythmias (nodal tachycardia and paroxysmal tachycardia with Wolff-Parkinson-White syndrome) the ectopic rhythm was the only finding which suggested the presence of some obscure type of congenital cardiac abnormality.

Routine electrocardiographic studies in infants and in congenital cardiac disease would probably reveal more frequent evidence of disturbances of cardiac rhythm and conduction associated with congenital cardiac anomaly. Up to now, disturbances of cardiac rhythm and conduction have been reported relatively infrequently in congenital cardiac disease. In all likelihood, they constitute an important aspect of the problem. In two of the five cases of this series, the arrhythmia or cardiac conduction disturbance contributed directly to the death of the patient. In a third case, the ectopic rhythm produced severe cardiac failure.

WENDKOS

Burke, E. C., Kirklin, J. W., and Edwards, J. E.: Sites of Obstruction to Pulmonary Blood Flow in The Tetralogy of Fallot: An Anatomy Study. Proc. Staff Meet., Mayo Clin. **26:** 498 (Dec.), 1951.

An anatomic study was made of 48 hearts with the tetralogy of Fallot to determine the types and incidence of obstruction to pulmonary blood flow. Twenty-two cases were observed personally, and in 26 instances descriptions of specimens were taken from the literature. In 43 of the 48 cases significant stenosis existed in the infundibulum either as the only site of obstruction to pulmonary blood flow or coupled with obstruction at the pulmonary valve. Significant obstruction at the level of the pulmonary valve occurred in 29 of the 48 cases. This obstruction was either restricted to the pulmonary valve or associated with stenosis at the infundibulum. Three cases showed atresia of the pulmonary trunk.

SIMON

Elster, B. B., and Eisenstadt, H. B.: Prolonged Anticoagulant Therapy for Ambulatory Patients. Texas J. Med. **48:** 14 (Jan.), 1952.

It will take considerable time before the clinical usefulness of prolonged dicumarol treatment can be appraised fully because of the divergences and variabilities shown by the diseases for which it is indicated. However, regardless of the final value of dicumarol therapy, it can be stated that the administration of this drug during a long or even an indefinite period can be regulated safely by careful clinical examinations and simple laboratory procedures available to the general practitioner. This observation is in contrast with some of the early and even more recent reports about dicumarol toxicity which mention serious and even fatal hemorrhages.

An attempt has been made to outline the clinical applications of prolonged anticoagulant therapy with dicumarol. By reducing the blood coagulability, the dangers of thromboembolism can be lessened greatly. Because of possible complicating hemorrhages, a simplified method of controlling the hypocoagulability is emphasized and described.

BERNSTEIN

CONGESTIVE HEART FAILURE

Berenson, G. S., and Burch, G. E.: The Response of Patients with Congestive Heart Failure to a

Rapid Elevation in Atmospheric Temperature and Humidity. Am. J. M. Sc. **223:** 45 (Jan.), 1952.

The effect of changes in climatic surroundings upon the condition of patients with mild congestive heart failure was determined, and the responses compared to a group of control subjects exposed to the same changes in environmental temperature and humidity. A controlled observation room was employed to produce climatic changes while clinical data were obtained referable to the cardiac, circulatory and psychic responses. The variations in temperature and humidity were produced suddenly, and were of short duration, so that acclimatization did not occur.

Significant changes noted among the control subjects included peripheral vasodilation, increasing pulse pressure, rising skin temperatures, tachycardia, tachypnea, and slight dyspnea. They became irritable, nervous, and noted headaches and tremors. The subjects with congestive heart failure were unable to tolerate the hot and humid atmosphere for as long a period as controls. These patients became very dyspneic and apprehensive. The symptoms and signs of left ventricular failure reappeared with rales, venous engorgement, gallop rhythm, and cardiac asthma. In general, cardiac murmurs, when present, were accentuated. The return to basal state, when removed from the hot, humid atmosphere, was slower in the cardiac than in the control subjects.

It is suggested that the increase in respiratory rates noted in both may be a response of the body to eliminate heat by convection and volatilization of water from the lungs; or it may be due to increased oxygen needs associated with an increase in metabolism. The authors suggest that greater use of air conditioning may be necessary in wards and hospitals to help cardiac patients to combat environmental heat.

SHUMAN

Prentice, T. C., Berlin, N. I., Hyde, G. M., Parsons, R. J., Lawrence, J. H., and Port, S.: Total Red Cell Volume, Plasma Volume, and Sodium Space in Congestive Heart Failure. J. Clin. Investigation **30:** 1471 (Dec.), 1951.

The blood volume of 27 patients with congestive heart failue was determined with P^{32}-labeled cells. The total red cell volume is determined, and the total blood volume and plasma volume are calculated from this value and the venous hematocrit. The authors point out the likelihood that venous hematocrit does not differ significantly from "total body hematocrit."

Total exchangeable body sodium was determined by the administration of Na^{24} and the measurements of plasma radioactivity 18 hours after administration. Twelve of 27 patients had normal blood volume, total red cell volume and plasma volume. In 11 of these 12, congestive failure was due to either arteriosclerotic or hypertensive heart disease; one was a patient with old rheumatic valvulitis.

The remaining 15 had either an elevated blood volume, total red cell volume, or plasma volume. Seven of these had rheumatic valvulitis, while eight had hypertensive or arteriosclerotic heart disease. In the seven with rheumatic heart disease total blood volumes were markedly increased, total red cell volume and plasma volume rising to an equal extent; in the other eight the blood volume was only slightly increased with marked variation from patient to patient in red cell and plasma volume changes.

In five of six patients so studied, the blood volume increased when compensation occurred; in the sixth case the blood volume decreased with the return of compensation.

It was noted that serum sodium concentration did not change markedly during heart failure, although total body sodium rose to a marked degree.

The finding of a normal or only minimally increased blood volume in most patients in frank cardiac decompensation requires a re-examination of some of the current concepts of the physiology of congestive failure.

WAIFE

Davies, C. E.: The Effect of Treatment on the Renal Circulation in Heart Failure. Lancet **261:** 1052 (Dec.), 1951.

The renal circulation has been studied in congestive heart failure due to rheumatic heart disease or chronic lung disease. The renal blood-flow was reduced in both groups. Intravenous digoxin had no immediate effect on the renal circulation or on the rate of sodium excretion in either group.

In rheumatic heart disease, long-continued treatment, leading to considerable clinical improvement, was not accompanied by any significant change in the renal circulation, and the ability to excrete salt remained severely impaired. Recovery from pulmonary heart failure, on the other hand, was accompanied by a considerable increase of renal blood-flow and a small increase of glomerular filtration-rate, and at the same time the capacity to eliminate salt appeared to be restored to normal. Anoxia, venous congestion, and pulmonary hypertension do not seem to be factors initiating the disturbance of renal function. Hormonal factors may be important, but the evidence is scanty.

BERNSTEIN

Eichna, L. W., Farber, S. J., Berger, A. R., Earle, D. P., Rader, B., Pellegrino, E., Albert, R. E., Alexander, J. D., Toube, H., and Youngwirth, S.: The Interrelationships of the Cardiovascular, Renal and Electrolyte Effects of Intravenous Digoxin in Congestive Heart Failure. J. Clin. Investigation. **30:** 1250 (Nov.), 1951.

The authors attempted to answer two questions:

(1) Do renal hemodynamics improve concomitantly with the known improvement in cardiovascular dynamics? (2) What is the relationship of the ensuing diuresis to the general cardiovascular and renal hemodynamic effects? Detailed studies were performed on five patients with congestive heart failure in decompensation, by means of cardiac output studied by the direct Fick method, blood volume by the Evans blue dye, and renal clearance studies. After a 45 minute control period 1.0 mg. to 1.5 mg. of digoxin, in 5 per cent dextrose, was injected into a peripheral vein or the right atrium.

Digoxin produced considerable subjective improvement in all five patients with clinical relief becoming apparent from 20 to 30 minutes after the injection. The cardiovascular effects which were noticed consisted of ventricular slowing, increased cardiac output, increased oxygen content of the mixed venous blood, decreased A-V oxygen difference, decreased peripheral venous and right atrial pressures, decreased right ventricular and diastolic pressure, decreased pulmonary diastolic pressure, and widened femoral arterial pressure. The blood volume did not change. These changes occurred rapidly and simultaneously and it was not possible to determine the site of the primary action of digoxin.

The changes in renal plasma flow and glomerular filtration rate were less consistent, smaller in absolute values, and slower in onset and progression. They generally were slightly increased from one and one-half to two hours after the drug. However, the urine flow and the rate of sodium and chloride excretion (to a lesser extent potassium excretion) increased promptly and continued to increase markedly and progressively.

The diureses were not consistently related to improvement in renal hemodynamics but appeared more closely associated with changes in the renal vascular pressure, as shown by increased arterial pulse pressure and decreased systemic venous pressure.

WAIFE

Friedman, I. S.: Problems of Cation-Exchange-Resin Therapy, Arch. Int. Med. **89:** 99 (Jan.), 1952.

The use of cation-exchange resins may result in disturbances of the acid-base balance of the body and the loss of essential cations and other necessary substances. Hyperchloremia, acidosis, and elevation of the blood urea nitrogen were most commonly observed. Hypopotassemia and hypocalcemia may also occur. As yet, studies pertaining to the loss of magnesium, the vitamins of the B complex, and medicaments have not been done.

Granular casts form in the urine of all patients who are given effective doses of the resins. No ill effects due to these casts have been noted. All patients, particularly those with renal involvement, require careful supervision and blood electrolyte determinations during exchange-resin therapy. To avoid the development of depletion states, supplements of potassium, calcium, magnesium, and the vitamins of the B complex should be given to these patients.

BERNSTEIN

CORONARY ARTERY DISEASE, MYOCARDIAL INFARCTION

Master, A. M., and Jaffe, H. L.: Complete Functional Recovery After Coronary Occlusion and Insufficiency. J.A.M.A. **147:** 1721 (Dec. 29), 1951.

The authors studied the progress of 412 patients after acute coronary occlusion and 141 patients after acute coronary insufficiency. About two-fifths of the patients with coronary occlusion have made a complete recovery. Another one-fourth made satisfactory recovery, but experienced occasional angina of effort. Twenty-five per cent who recovered completely have lived more than 10 years, and 40 per cent more than five years. Eighty-three per cent are employed and of these 60 per cent are at full-time work. Whether the infarct had been anterior or posterior did not influence the future course of the patient. Twenty-six patients had recovered complete function, although the heart was greatly enlarged and/or the electrocardiogram was very abnormal. In 10 patients, definite evidence of ventricular aneurysm was present. One of these patients is well 29 years after the attack.

The authors feel that following coronary occlusion the best prognostic guide appears to be the patient's symptoms rather than the objective findings. Twenty-six additional patients made a complete functional recovery but died subsequently, the great majority after 5 to 10 years. Of the patients who made complete functional recovery only six (3 per cent) died in less than five years. The mortality rate in patients who made a complete recovery was less than half that found in those who continued to have symptoms. Patients in whom the attack occurred before the age of 45 did only slightly better than did the older patients.

The authors feel that the prognosis following acute coronary insufficiency was even better than that after coronary occlusion, as over half the former patients made a complete recovery and only 4 per cent of them have died. The majority of patients who survive an attack of coronary occlusion or insufficiency are able to lead fairly normal lives and to be gainfully employed. To avoid much of the psychologic and physical invalidism which exists they should be encouraged to go back to work and live normal lives as soon as is physically possible.

KITCHELL

Russek, H. I., Zohman, B. L., Doerner, A. A., and Russek, A. S.: Age and Survival in Cases of Acute

Myocardial Infarction. J.A.M.A. **147:** 1731 (Dec. 29), 1951.

The authors studied age and mortality in a group of 1,047 persons with acute myocardial infarction. From the clinical findings in the first 24 hours of hospitalization, the cases were classified as good risks or poor risks. The poor risks were those who had had (1) previous myocardial infarction, (2) intractible pain, (3) severe degree or persistence of shock, (4) significant enlargement of the heart, (5) gallop rhythm, (6) congestive heart failure, (7) auricular fibrillation, ventricular tachycardia or intraventricular block, and (8) diabetic acidosis or other serious complicating disease.

The mortality rate in 618 subjects under 60 years of age was 28.8 per cent, whereas the mortality rate in 429 subjects 60 or older was 40.1 per cent. The mortality rate among 331 good risk patients under 60 was 3 per cent, while that among 358 similar patients 60 or older was almost identical (3.2 per cent). Among 287 patients under 60 who showed poor risk criteria on the first day of admission the mortality rate was 58.5 per cent as compared with 61.6 per cent among 271 older patients who also showed poor prognostic signs.

The authors feel that age in itself has little to do with the outcome of the individual case. They feel the higher mortality rates from acute myocardial infarction observed in older age groups are due to a greater frequency of serious attacks, probably as the result of senile deterioration of the myocardium.

KITCHELL

Silber, E. N., Levin, B. D., Becker, G. H., and Levy, R. C.: Treatment of Shock in Recent Myocardial Infarction by Intra-arterial Transfusion. J.A.M.A. **147:** 1626 (Dec. 22), 1951.

Although significant reduction in the early mortality following myocardial infarction resulted from the routine use of anticoagulants, the treatment of recent myocardial infarction remains inadequate in cases where a clinical picture of profound shock is present. The authors report nine cases chosen for treatment because of typical histories, unequivocal electrocardiographic evidence of recent myocardial infarction, and the presence of a clinical picture of severe shock.

In six of these nine cases the blood pressure was zero immediately prior to transfusion. In the remaining cases the systolic pressure was 95 mm. or less, and in no case was the pulse pressure greater than 30 mm. Intra-arterial transfusion requires only a relatively small amount of blood to restore rapidly the blood pressure and a normal circulating blood volume. Such transfusion, by its improvement of coronary flow, tends to relieve hypoxia and to restore the normal contractile power to that portion of the myocardium that has not been infarcted. It results in prompt stimulation of the respiratory centers and a prompt improvement of respiration and restoration of a normal sensorium. Finally, intra-arterial transfusion provides for the rapid return of kidney function by re establishing an adequate filtration pressure. Although seven of the nine cases died from their disease, the authors feel that treatment is sufficiently promising to warrant further investigation.

KITCHELL

Beck, C. S., Hahn, R. S., Leigninger, D. S., and McAllister, F. F.: Operation for Coronary Artery Disease. J.A.M.A. **147:** 1726 (Dec. 29), 1951.

A two-stage operation is described. The first stage consists in the placement of a free vein graft between the coronary sinus and the aorta. The second stage consists of partial ligation of the coronary sinus at the ostium of the sinus into the right auricle. The authors have evidence to show that oxygenated blood delivered into the venous system of the heart can protect the heart against occlusion of a major coronary artery.

The first stage of the operation provides a fistula from the aorta through the graft and into the coronary sinus. Most of the blood escapes into the right auricle. The flow is as rapid as in an arteriovenous fistula elsewhere. A thrill is palpable over the graft. The second portion of this operation reduces the lumen of the sinus from 3.5 mm. to 2 mm. in various patients. The authors feel a considerable quantity of blood can flow through such an opening, but results indicate the flow is not great enough to produce clinical manifestations of a fistula except for the murmur and thrill.

They report the results on a series of 28 patients. There were 23 recoveries and 5 deaths, a mortality rate of 18 per cent. The authors feel the period of time involved is not sufficient for them to make a clinical evaluation but so far the results appear to be, or actually are, favorable. In the development of this operation years were devoted to experimental work on dogs and the benefit was indeed significant. They state the operation on patients has not been completely developed and the problem of thrombosis exists in some cases. Before a real evaluation is made of the procedure, the authors feel the operation will have to be done on additional patients.

KITCHELL

Hannigan, C. A., Wroblewski, F., Lewis, W. H., Jr., and La Due, J. S.: Major Surgery in Patients with Healed Myocardial Infarction. Am. J. M. Sc. **222:** 628 (Dec.), 1951.

The present improved status of major surgery in patients with myocardial infarction has been achieved by advance in pre- and postoperative management, anesthetic technics and the use of fluid and antibiotic therapy. In this study, 58 patients with definite clinical and electrocardiographic evidence of myocardial infarction were observed during and after major surgical procedures in order

to evaluate the incidence of cardiorespiratory complications and the ability of these patients to tolerate surgery. The mortality rate in the entire group was 5.2 per cent; the three deaths were ascribed to postoperative tracheitis, myocardial infarction, and to operative shock.

The total incidence of cardiorespiratory complications was 24.1 per cent; four patients developed new infarctions; four had bronchopneumonia; one had a pulmonary embolus, and five showed congestive heart failure. Cardiac enlargement and congestive heart failure were factors which apparently increased the incidence of complications. However, the presence of hypertension, age of the patient, or the infarct had no bearing on the incidence of cardiorespiratory complications.

The use of pentothal anesthesia was associated with a high complication rate while spinal and local anesthesia were well tolerated. The duration of surgery was an important factor; 37.5 per cent of patients undergoing surgery longer than three hours suffered complications. Whole blood and fluids were well tolerated.

Major surgery for cancer should not be withheld from the patient who has a healed myocardial infarction. Existing heart disease does not appear to be adversely affected by such surgery.

SHUMAN

Chapman, D. W., Skaggs, R. H., Thomas, J. R., and Greene, J. A.: The Effect of Cortisone in Experimental Myocardial Infarction. Am. J. M. Sc. **223:** 41 (Dec.), 1951.

Myocardial infarction was produced by ligation of the left anterior descending coronary artery of dogs following which cortisone was administered for 10 day intervals. Infarctions were produced in another group which received no cortisone treatment. The adequacy of cortisone therapy was evaluated by means of eosinophil counts which showed a persistent fall in the treated group, whereas the counts returned to normal following recovery from operation in the control animals.

The result of this study indicated that cortisone had no deleterious effect upon the infarction either from the standpoint of size of the lesion or its rate of healing. No electrolyte disturbances were noted in these experiments. There was slight evidence of adrenal cortical atrophy after 10 days of cortisone therapy; however, 20 days after cessation of cortisone therapy the adrenals were normal. From this study, it would appear that cortisone is not contraindicated in the presence of myocardial infarction in dogs.

SHUMAN

Blumgart, H. L.: Coronary Disease: Clinical-Pathologic Correlations and Physiology. Bull. New York Acad. Med. **27:** 693 (Dec.), 1951.

In this survey article the author discusses the unique physiologic characteristics of the coronary circulation and their clinical significance. The injection dissection method of Schlesinger has been employed in the study of over 1600 hearts during the past 10 years, and the results have given further insight into the meaning of the clinical signs and symptoms of coronary heart disease.

In the normal heart the coronary arteries are functionally end arteries and fine anastomotic communications have only very limited significance in preventing myocardial damage due to sudden coronary narrowing or closure. However, this anastomotic circulation does develop in certain situations, and is an explanation for the fact that complete occlusion or considerable narrowing of one or more coronary arteries may be present without producing any clinical signs or symptoms of myocardial damage.

The pathology and physiologic phenomena of angina pectoris, coronary failure and acute myocardial infarction are discussed. The underlying mechanism in these syndromes apparently is a relative disproportion between the myocardial blood demand and the supply afforded through the coronary vessels. The changes which result in the myocardium are due solely to the extent and duration of the relative ischemia and not to its etiology.

Treatment of these conditions should be aimed at correcting the ischemia or reducing its extent by measures designed to reduce the work of the heart in the presence of prolonged cardiac pain. This may limit the extent of myocardial necrosis or prevent its development and also favors the extension of a more adequate collateral circulation.

SAGALL

Cole, S. L., and Sugarman, J. N.: Cerebral Manifestations of Acute Myocardial Infarction. Am. J. M. Sc. **223:** 35 (Jan.), 1952.

Symptoms referable to the central nervous system, including syncope, convulsions, coma and hemiplegia, may dominate the clinical picture in acute myocardial infarction. Six patients with such manifestations are presented to show that the cardiac process may be overlooked when associated with cerebral symptomatology. Autopsy was performed in five, and disclosed no evidence of cerebral thrombosis, embolism or hemorrhage in the head examinations. An additional 15 patients are presented in whom autopsy had revealed combined myocardial infarction and cerebrovascular accident.

The authors suggest that generalized cerebral manifestations in the former cases may be induced by ischemia and anoxia following a drop in blood pressure associated with coronary occlusion. Focal neurologic findings may be the result of segmental narrowing and arterial insufficiency produced by cerebral arteriosclerosis. An attempt is made to differentiate the picture of acute myocardial in-

faction with central nervous system symptoms from the combined lesions of brain and heart.

SHUMAN

ELECTROCARDIOGRAPHY

Ljung, O.: Alterations in the Electrocardiograms as a Result of Emotionally Stimulated Respiratory Movements Especially with Reference to the So-called "Fright Electrocardiogram." Acta med. scandinav. **141:** 221 (Dec. 12), 1951.

The author observed more than 200 patients whose electrocardiograms were recorded before and after mild fright. In 10 patients there were alterations in the S-T segment or T waves, or both, which were considered pathologic or borderline. It is considered that the changes result from a reflex coronary spasm with myocardial hypoxemia, or some reflex effect upon the myocardium without either coronary spasm or hypoxemia.

The possibility that changes of this type are due to hyperventilation or to respiratory movements was investigated in this study by recording the electrocardiograms in 33 normal women with labile vegetative nervous systems during control periods, with the breath held in the deep inspiratory position for 5 to 10 seconds, and after two minutes of moderate hyperventilation. Sixteen healthy soldiers without vasomotor lability and six vegetatively labile subjects who had demonstrated alternating pathologic and normal electrocardiograms over a long period of time were examined in the same way.

The conclusion from these studies was that respiratory movements in response to emotional stimulation are by themselves only very occasionally the explanation for the so-called "fright electrocardiogram."

ROSENBAUM

Leitner, St. J., and Weber, E.: Investigations on Changes in the Electrocardiogram Following Injection of Histamine and Antistine. Helvet. med. acta **6:** 593 (Dec.), 1951.

The authors report changes of the electrocardiogram (tachycardia, depression of S-T segment and lowering of T-wave) observed in 22 persons following subcutaneous injection of 1 cc. histamine (in 1:1000 solution). These alterations disappeared when an antihistaminic (Antistine) was injected in a dose of 100 mg. subcutaneously or intravenously, two minutes following, or together with histamine.

The authors feel that these experiments are of practical importance since, in the course of various infections, allergic processes (with formation of histamine) develop, involving the myocardium, which could perhaps be prevented by the use of antihistaminics.

PICK

Oram, S., Holt, M., and East, T.: Esophageal and other Leads in Posterior Cardiac Infarction Brit. Heart J. **13:** 475 (Oct.), 1951.

Twenty-eight normals, 27 with posterior infarction, 42 with an equivocal lead III associated with a history of cardiac pain, 19 with equivocal lead III unaccompanied by cardiac pain, and 10 with left ventricular enlargement without a history of pain were studied by esophageal, deep epigastric and back-foot leads in an attempt to assess the importance of QS and negative T waves in lead III and to compare them with V_F.

The esophageal lead at ventricular levels varies within a wide normal range and a wide transition zone which may be difficult to distinguish from the abnormal. Many artefacts may occur. A simulated S-T segment elevation may occur.

The electrocardiographic diagnosis of infarction was based upon the presence of a Q wave at least 0.04 second in duration and a depth at least one-fourth the amplitude of R. By these criteria, of the 27 infarcts, 24 were diagnostic in the standard and 23 in the esophageal leads. Of the 42 with cardiac pain and equivocal lead III, V_F was positive in 18 and the esophageal in 11. In 19 without pain and equivocal lead III, V_F was positive in three and the esophageal in four. The 10 with left ventricular hypertrophy were negative in both V_F and esophageal leads.

There is no reason to employ esophageal leads in the diagnosis of posterior infarction.

SOLOFF

Welsch, A., and Spang, K.: The Diagnosis and Significance of the So-called Incomplete Right Bundle Branch Block in the Electrocardiogram. Arch. Kreislaufforsch. **17:** 326 (Dec.), 1951.

The authors present an analysis of 100 cases with the following electrocardiographic criteria: A second R wave in V_1, V_2 and V_E, and the QRS duration not more than 0.10 second in the limb leads and not more than 0.11 second in any precordial lead. The criteria of incomplete right bundle branch block were: the second R wave was separated from the first by 0.01 to 0.03 second and a prominent or widened S wave was present in the left precordial leads.

Incomplete right bundle branch block was found most frequently in cases with valvular disease, pulmonary or pulmonary vascular disease, in thorax deformities, in coronary disease, especially with infarction of the intraventricular septum, and in various other conditions with involvement of the right ventricle. The condition is rarely present in cases without any evidence of heart disease, and may then be due to an anomalous course of the conduction system.

A tall second R wave (>1 mV.) in the right precordial leads and an especially deep S wave in V_6 indicates right ventricular hypertrophy associated with the conduction defect. A tall R wave in left precordial leads may be considered as concomitant

left ventricular hypertrophy. The first upright deflection in V_1 is absent and the second delayed in the case of anteroseptal infarction.

Vectorial analysis of electrocardiograms of the described type reveals that the second late upright wave in the right precordial leads is due to rotation of the terminal portion of the vector loop in forward direction and towards the right. Since such an anomalous course of the vector loop may also be associated with changes in the position and form of the heart, the described pattern of incomplete right bundle branch block need not necessarily indicate an actual delay of intraventricular conduction.

PICK

Manning, M., and Yu, P. N. G.: Electrocardiographic Changes in Poliomyelitis. Analysis of 150 Cases. Am. J. M. Sc. **222:** 658 (Dec.), 1951.

Serial electrocardiograms were obtained during the course of treatment of poliomyelitis occurring in 150 patients. Of this group, only nine adults and 25 children had normal tracings throughout the illness. The abnormalities appearing in the remaining 116 patients consisted mainly of abnormal T waves, sinus tachycardia and prolonged Q-T intervals. In addition, several patients showed either premature ventricular contractions, or prolongation of the P-R interval, or lowering of the RS-T segment transiently.

The findings suggested that adults or patients with bulbar poliomyelitis were more prone to show electrocardiographic changes than those with other types of paralysis. Serum potassium studies performed on 91 patients showed an elevation over 6 mEq. per liter in 11 instances of which two had high peaked T waves in leads V_1 to V_3. There were eight autopsied cases of which only two revealed the presence of myocarditis. Pulmonary complications of infarction or bronchopneumonia and dilatation of the right ventricle were noted in four of the autopsied cases.

The electrocardiographic changes were considered to be nonspecific and were found to revert to normal within the first four weeks in the majority of cases.

SHUMAN

Binet, L., Strumsa, M. V., and Vernant, P.: Ventricular Fibrillation of Reoxygenation. Compt. rend. Soc. biol. **145:** 866 (June), 1951.

The onset of artificial or spontaneous breathing following anoxia, produced experimentally in the dog, is usually associated with more or less marked bradycardia. If the apnea is long and the anoxia severe, paroxysmal ventricular tachycardia may set in. Although these alterations of cardiac rhythm are, as a rule, transient and of benign character, the authors did observe in three experiments transition into fatal ventricular fibrillation, resistant to all therapeutic attempts. In one animal, this event was seen despite preceding section of the vagal nerves. This is evidence that the fibrillation does not develop in consequence of increased vagal tone during anoxia. Hyperadrenalemia, on the other hand, could not be excluded as a precipitating factor.

PICK

Magendantz, H., and Shortsleeve, J.: Electrocardiographic Abnormalities in Patients Exhibiting Anxiety. Am. Heart J. **42:** 849 (Dec.), 1951.

The authors noted minor but definite RS-T segment and T-wave changes in the electrocardiograms of some hospitalized patients not known to have heart disease. RS-T segments were abnormally deviated from the isoelectric line; T waves were small, flat or showed abnormal direction.

Careful clinical and laboratory re-examination of these patients showed no heart disease. The authors suspected that anxiety resulting from the procedure of taking the electrocardiogram caused these changes. Electrocardiograms were repeated on the following day after reassurance to the patient, and 95 minutes of rest. "Surpris'ngly often" this led to reversal of the RS-T and T changes.

Clinical information on 22 selected cases is presented. Eighteen had discharge diagnoses of psychiatric disease; the remaining four had diagnoses not related to the cardiovascular system. In this particular series hyperventilation, rapid (or change in) heart rate, exercise, time of day and absorptive state were eliminated as possible causes. The electrocardiographer is urged to be cautious in diagnosing heart disease on the sole evidence of such electrocardiographic abnormalities, particularly in the young.

HELLERSTEIN

Doumer, E., and Dumez, L.: Familial Type of Wolff-Parkinson-White Syndrome. Wolff-Parkinson-White Syndrome with Apparently Normal P-R in Certain Leads. Arch. mal. coeur **44:** 1134 (Dec.), 1951.

The authors observed two members of a family (mother, 63 years, and son, 35 years) with attacks of paroxysmal tachycardia and the electrocardiographic syndrome of Wolff-Parkinson-White. The mother's tracing showed the typical contour in all leads, while the electrocardiogram of the son revealed right axis shift with typical Wolff-Parkinson-White complexes in leads III, aV_F and right sided chest leads, and apparently normal P-R and QRS in lead I. The presence of pre-excitation could be proved in esophageal leads and vectorcardiograms. These also showed that the anomalous initial component of QRS (delta wave) had a strictly vertical direction and, therefore, was not reflected in leads I and V_6.

The authors feel that certain electrocardiographic tracings, which show ventricular preponderance or a pattern of bundle branch block only in single leads,

in the absence of clinical evidence of heart disease, could be explained on a similar basis.

PICK

Donzelot, E., and Milanovich, J. B.: A Rational Order of Frontal Electrocardiographic Leads. Arch. mal. coeur **44:** 1141 (Dec.), 1951.

The authors feel that the conventional arrangement of leads taken in the frontal plane (first I to III, then aV_R, aV_L and aV_F) is not logical compared with leads in the horizontal plane (V_1 to V_6), which are arranged in the natural order of development of positivity and negativity.

In order to facilitate the reading of frontal leads, and in accordance with the development and the direction of the vector loop, they recommend the following order: aV_L—I—($-aV_R$)—II–aV_F—III. Arranged in such a system, the axis of each lead differs from its neighbour by 30 degrees; the axis halving the 60 degree angle between lead I and II, which is not represented in the conventional electrocardiogram, is obtained by lead aV_R taken with reversed polarity ($-aV_R$).

PICK

Levine, H., Nahum, L. H., Geller, H. M., and Sikand, R. S.: Genesis of the Electrocardiographic Pattern of Digitalis. Am. J. Physiol. **167:** 726 (Dec.), 1951.

Two current explanations for the electrocardiographic digitalis pattern are (a) shortening of the Q-T interval with attendant changes in the order of recovery, (b) acceleration of repolarization in subendocardial layers. The authors present evidence to support the concept that slowing of repolarization in the apical region is the basic mechanism for production of the digitalis pattern.

In the precordial leads S-T is depressed and T at first depressed and then inverted. VF shows depression of S-T and inversion of T. V_R presents an elevation in S-T and an upright T. An upright T appears when recovery in the proximal zone of that lead precedes recovery in the distal zone and vice versa. Flattening and inversion of T in V_F indicates that its proximal zone (apex) is now repolarizing more slowly than the distal zone (base). This could be explained either by slowing at the apex or acceleration at the distal base in this lead. This pattern is similar to that obtained when the apex is cooled and its repolarization slowed. Measurements of Q-T interval indicated no shortening of the slowest fibers to recover, which are at the base.

Both of these findings support the concept of slow repolarization at the apex as responsible for production of the digitalis pattern. When ectopic beats occur they have a configuration which has been shown to originate near the left apex. Artificial hyperpyrexia, which accelerates apical repolarization, abolishes the digitalis pattern.

OPPENHEIMER

Arrelaga, F. C., and Soldati, L.: The Electrocardiogram in Subacute Nonvascular Cor Pulmonale. Arch. mal. coeur **44:** 1088 (Dec.), 1951.

The authors describe an electrocardiographic pattern which, in their opinion, is specific for "subacute, nonvascular cor pulmonale." It was observed in six instances, two of which had clinical signs of chronic cor pulmonale with "bronchogenic exacerbation," and four who had bronchial asthma without clinical signs of cardiac involvement.

The characteristic electrocardiographic features are tachycardia, a pointed P wave in leads II, III and aV_F (right axis shift of P) in association with left axis shift (-20 degrees to -115 degrees) of QRS. R is prominent in aV_R and S in all precordial leads with exception of V_1; in two instances the intrinsicoid deflection was delayed and in one instance T inverted in the latter lead.

The described electrocardiographic changes disappeared in five cases within two weeks, together with clinical improvement. Their development may be ascribed to a combination of factors, namely, acute right heart dilatation, an anomalous position of the heart and transient myocardial hypoxia. The electrocardiogram is of value in differentiating such cases from instances of true chronic cor pulmonale, or from cases with dyspnea due to heart failure ("cardiac asthma").

PICK

Grishman, A., and Jaffe, H.: Spatial Vectorcardiography: Wide QRS Complexes with Short P-R Interval (the Wolff-Parkinson-White Syndrome). J. Mt. Sinai Hosp. **18:** 208 (Nov.–Dec.), 1951.

The vectorcardiograms and electrocardiograms of four out of nine studied cases of Wolff-Parkinson-White syndrome were presented. In each case the vector cardiograms revealed the vector loop to be directed to the left, either anteriorly or posteriorly. The initial portion of the centrifugal loop was closely spaced, this initial slow segment corresponding to the delta wave in the electrocardiogram. The T loop was discordant to the QRS loop. One patient with a myocardial infarction and intermittent Wolff-Parkinson-White conduction showed the same vectorcardiogram as patients with this syndrome without organic heart disease. Another patient with pulmonic stenosis whose vectorcardiogram was typical of the Wolff-Parkinson-White syndrome, showed esophageal leads corresponding to the sagittal projection of the special vectorcardiogram, all leads except E_1 being negative. When abnormal conduction in this case was abolished by quinidine lactate intravenously, the electrocardiogram showed marked right ventricular hypertrophy, and esophageal leads revealed disappearance of the delta waves and suggested an entirely different spatial orientation of the cardiac vector.

The evidence provided by spatial vectorcardiography supports the theory that in Wolff-Parkinson-

White syndrome, the excitation wave spreads to both ventricles along accessory pathways. There is a wave front arising at the right posterior portion of the atrioventricular groove, progressing to the left anteriorly, laterally, or slightly posteriorly, and in a superior or inferior direction. Because there is a wave front accession of the electromotive forces without instantaneous balance of the forces of the right and left ventricles, of the anterior and posterior walls or across the septum, it is impossible to make the diagnosis of anterior or diaphragmatic infarction, since an abnormal "infarction vector" depends upon a lack of balance of forces between the infarcted areas and the wall opposite. Similarly enlargement of either ventricle cannot be detected.

CORTELL

ENDOCRINE EFFECTS ON CIRCULATION

Ferayorni, R. R., and Sprague, R. G.: Myxedema with Ascites and Hydrothorax. Proc. Staff Meet., Mayo Clin. **27:** 25 (Jan.), 1952.

Although myxedema sometimes may result in ascites, hydrothorax or hydropericardium, serous effusions in myxedema are relatively rare. In the present case evidence of heart failure was lacking, and the subsidence of effusions during treatment with desiccated thyroid may be considered as prima facie evidence that the effusions were in fact dependent on the myxedema.

The outcome in this case suggests that the patient had inadequate coronary circulation at the time he was under observation. However, if this condition had played a large part in the production of the hydrothorax and ascites, the effusions would not have cleared with treatment for the myxedema alone.

SIMON

Leriche, R., Beaconsfield, P., and Boely, C.: Aortography: Its Interpretation and Value. A Report of 200 Cases. Surg., Gynec. & Obst. **94:** 83 (Jan.), 1952.

The authors state that aortography should not be considered a routine practice in the medical investigation of patients with peripheral vascular disease. It is employed only after simpler methods have not disclosed information necessary for the best management of the patient.

The indications follow: (1) Obliterative arteritis in which the femoral pulse is absent; (2) aneurysms or arteriovenous fistulas; (3) embolism of the aorta or its main branches; (4) patients undergoing rectal surgery, who are known to have obstructive peripheral vascular disease, to assess the condition of the pelvic vessels and collaterals which might be interfered with during operation; (5) suspected renal or suprarenal tumors; (6) suspected placenta previa.

The contraindications are: (1) poor renal function; (2) danger of vasospasm in impending gangrene; (3) allergy to iodine; (4) poor physical condition.

The authors conclude that aortography is a procedure which may be carried out without risk to the patient, but its practical applications and values are limited. In peripheral vascular disease its use should be restricted to those patients in whom surgery is contemplated.

SCHWEDEL

HYPERTENSION

Moyer, J. H., Handley, C. A., and Huggins, R. A.: Some Pharmacodynamic Effects of 1-hydrazinophthalazine (C-5068) with Particular Reference to Renal Function and Cardiovascular Response. J. Pharmacol. & Exper. Therap. **103:** 368 (Dec.), 1951.

Hydrazinophthalazine is being investigated at the present time as a possible hypotensive agent in the treatment of essential hypertension. The present study reports observations on the renal function and the cardiovascular system in dogs after the parenteral administration of the drug. In unanesthetized dogs the renal blood flow was increased without concomitant increase in glomerular filtration rate or maximum tubular function, but with anesthetized animals the renal blood flow, glomerular filtration rate, and maximum tubular function were all depressed.

The cardiovascular effects consisted of a decrease in peripheral resistance, a lowering of blood pressure, a prominent tachycardia and an increase in cardiac output. The increase in renal blood flow was roughly proportional to the increased cardiac output. A significant peripheral adrenergic blockade accompanied by epinephrine reversal was shown after intra-arterial injection but could not be demonstrated in the dog extremity alone. This suggests that in the extremity neurogenic adrenergic blockade and vasodilatation are minimal, but that the hypotensive action of the drug must mainly be a function of vasodilatation of the splanchnic vascular bed.

The present study indicates that 1-hydrazinophthalazine theoretically would be an ideal agent in hypertension or in any disease associated with, or due to, renal ischemia, but its usefulness may be limited by the concurrent tachycardia and increased cardiac output.

SAGALL

Smithwick, R. H.: Effect of Thoracolumbar Splanchnicectomy on Mortality and Survival Rates. J. A. M. A. **147:** 1611 (Dec. 22), 1951.

Since 1938 approximately 3,000 patients have been considered for surgical treatment. About two-thirds have been operated on and one-third have been treated medically. Most of these cases have not been followed long enough to be included in the discussion at present. This report is on the mortality and survival rate of the first 892 patients in this series to have thoracolumbar splanchnicectomy.

They were seen between 1938 and 1946 inclusive and have been followed at least four, and at most

12, years. The present report deals with 296 patients who were not operated on and 596 who were. Smithwick divides all these patients into four groups according to his criteria. The follow-up shows that the prognosis for cases in groups 2, 3, and 4 (his classification) has been significantly improved by thoracolumbar splanchnicectomy. The patients who derived the greatest benefit were those in groups 2 and 3.

Smithwick concludes the effect of surgical treatment on prognosis affords the only reliable basis so far developed for the selection of cases for splanchnicectomy. The survival curves for patients who have had thoracolumbar splanchnicectomy should be useful in judging the relative merits of different forms of therapy in consecutive cases having varying amounts of cardiovascular disease when first seen.

KITCHELL

Goodman, H. L.: Malignant Hypertension with Unilateral Renal-Artery Occlusion. New England J. Med. **246:** 8 (Jan. 3), 1952.

The case of a 22 year old woman with malignant hypertension is described in detail. Death resulted from a massive right intracerebral hemorrhage with ventricular extension some three and one-half years after a bilateral lumbodorsal sympathectomy which failed to alter the hypertension significantly. The postmortem examination disclosed an old thrombotic occlusion of the right renal artery which was considered to be the initiating factor in the hypertension. The left kidney showed typical changes of malignant nephrosclerosis whereas the arterioles of the occluded kidney were completely spared. This finding was considered evidence that the occlusion of the renal artery preceded the hypertension. Since the clinical symptoms developed suddenly and progressed rapidly, a single etiology also seemed logical. The pathologic studies were believed to suggest that the right renal artery was occluded by an old thrombus rather than by an embolus.

ROSENBAUM

Kauntze, R., and Trounce, J.: Treatment of Arterial Hypertension with Veriloid, Lancet **6692:** 1002 (Dec.), 1951.

Veriloid by mouth will lower the blood pressure in about two-thirds of hypertensives. In half of these the hypotensive level may so closely approach the toxic level as to make its daily use out of hospital unsuitable; this leaves some 20 to 30 per cent in whom the drug is a satisfactory hypotensive agent. In this group well-being and freedom from symptoms may be complete, yet the dosage needs continuous supervision and the cooperation of an intelligent patient, since sensitivity may change after months of administration. On omission of veriloid the blood pressure returns to its former levels.

Phenobarbitone has been the most useful agent in diminishing toxic symptoms. It seems likely that toxic effects are an inseparable expression of the hypotensive qualities of the ester alkaloids in veriloid; they are, however, a safeguard against overdosage.

BERNSTEIN

Perera, G.: Endocrine Factors in Hypertension. Bull. New York Acad. Med. **28:** 43 (Jan.), 1952.

The author discusses the relationship of the psyche, stress and steroids to the production of hypertensive vascular disease, and points out that these factors may be related to various substances elaborated by endocrine glands. Certain endocrine secretions—epinephrine, norepinephrine, desoxycorticosterone and cortisone—have been shown to possess pressor qualities, but there is no definite proof of endocrine dysfunction in the etiology or subsequent course of hypertensive vascular disease. These hormones probably modify rather than initiate basic metabolic processes. In renal hypertension, pressor substances which are normally excreted may be retained, and in other cases unknown metabolites may sensitize blood vessels to normal amounts of hormone. Despite recent advances and theories, the problem of hypertensive disease still contains many unanswered questions.

SAGALL

PATHOLOGIC PHYSIOLOGY

Lucas, B. G. B.: Some Observations on Anoxia. Anesthesiology **12:** 762 (Nov.), 1951.

Central nervous system damage from anoxia appears to be the same regardless of the type or cause of the anoxia. An intracellular edema is the earliest change occurring in anoxic brain cells. If this edema is reabsorbed the cell will recover, but if not the edema will mechanically interfere with oxygen access and worsen the anoxia leading to death of the cell. This postanoxic edema may explain the accumulative effect of regular intermittent anoxia because the time interval between anoxic insults is not enough for the edema to be reabsorbed. Clinically, this may be applied to the problem of restoring cerebral oxygenation after cardiac arrest. The brain cells may die even though cerebral circulation is re-established after cardiac arrest unless some method of removing the intracellular edema is started.

The author believes the best method is the intravenous administration of concentrated human serum in a dose not exceeding 50 milliliters per hour. Prompt cardiac massage and artificial respiration constitute the best method of treatment of cardiac arrest under anesthesia. If the heart is in ventricular fibrillation the abnormal rhythm must be stopped by electrical defibrillation or arterial transfusions under sufficient pressure to force oxygenated blood into the coronary circulation. Anesthesia itself may be a state of histotoxic anoxia and thus add to the

effect of anoxia on the brain cells. Search should be directed at ways of making the brain more resistant to the effect of anoxia in order to overcome the irreversible effects of anoxic emergencies.

SAGALL

Veal, J. R., Dugan, T. J., Bauersfeld, R., and Russell, A. S.: The Physiologic Basis for Intra-arterial Transfusion in Severe Hypotension. South. M. J. **44:** 1096 (Dec.), 1951.

The authors compare the effects of treating experimental hemorrhage by the intravenous and intra-arterial routes of transfusion. The physiologic basis for intra-arterial transfusion in severe sustained hypotension is as follows: When the state of hypotension reaches a critical stage even large quantities of blood given intravenously may fail to restore the circulation. In fact it may cause complete failure by overloading the right heart.

To obtain forceful cardiac contractions and re-establish perfusion of the blood, the arterial pressure must be raised rapidly. This may be accomplished by intra-arterial transfusion. When blood is administered intra-arterially, at a pressure higher than that existing in the arterial bed, the blood will flow along the course of least resistance. It has been shown that it may fill the entire arterial system before an appreciable amount enters the veins. As soon as the aortic pressure is elevated, the intra-aortic resistance is increased and the heart pressure rises. This in turn allows better contractions and more forceful propulsion of blood into the aorta. By elevating the intra-arterial pressure the vasoconstriction is also relaxed and more adequate perfusion throughout the vascular bed results.

BERNSTEIN

Brown, E., Hopper, J., Jr., Sampson, J. J., and Mudrick, C.: Venous Congestion of the Extremities in Relation to Blood Volume Determinations and to Mixing Curves of Carbon Monoxide and T-1824 in Normal Human Subjects. J. Clin. Investigation. **30:** 1441 (Dec.), 1951.

The authors studied the limitations of blood volume determinations under conditions of venous stasis or congestion. The total carbon monoxide—available volume was measured. Congestion of the extremities of normal human subjects was induced by pneumatic cuffs inflated to pressures just below the diastolic pressure, which trapped as much as one-fourth of the total blood volume. This mass of pooled blood in the veins did not affect the measurement of total blood volume by the carbon monoxide method. It also did not cause delay in the mixing of T-1824 dye provided blood samples were taken at least 15 minutes following the introduction of the dye. Under these circumstances total, rather than "effective," blood volume is measured.

WAIFE

Deane, N., Schreiner, G. E., and Robertson, J. S.: The Velocity of Distribution of Sucrose between Plasma and Interstitial Fluid, with Reference to the Use of Sucrose for the Measurement of Extracellular Fluid in Man. J. Clin. Investigation **30:** 1463 (Dec.), 1951.

The authors have substituted sucrose for inulin in the measurement of extracellular fluid in man. Sucrose is not metabolized in man, and by means of a calibrated infusion, in which a priming injection is omitted, it was found that the mixing process is such that within 30 to 180 minutes after the beginning of the sucrose infusion the plasma is essentially in equilibrium with the interstitial fluid.

The method is a more practical approach to the problem of extracellular fluid measurement than that of the five-hour equilibration and total urine collection method. This method may be extended to pediatric patients. It has the advantage of revealing failure to obtain equilibration between plasma and extracellular fluid if the volume of distribution has not attained a maximal value by the end of the three-hour period. The method is not applicable in its present form to edematous patients without prolonging the infusion.

WAIFE

Kerper-Fronius, E., Varga, F., Vönöczky, J., and Kun, K.: The Relationship between Slowing of Circulation, Oxygen Deficit and Intoxication in Infants. Helvet. paediat. acta **5:** 377 (Nov.), 1951.

In 29 infants with acute dehydration, 31 cases of atrophy and in four cases of infantile pyloric stenosis the following determinations were made: oxygen saturation, carbon dioxide content and nonprotein nitrogen of the venous blood, and oxygen consumption.

This comparison showed that the known reduction of cardiac output in acute dehydration produces peripheral oxygen desaturation and signs of toxicity since the body requirement of oxygen remains unchanged, or is actually increased in this condition. On the other hand, in cases of pronounced atrophy or pyloric stenosis, the reduced circulation appears sufficient for the decreased metabolic requirements. Therefore, the latter patients do not appear "toxic" despite their circulatory failure. These observations meet several objections which can be raised against the "circulatory theory" of infantile toxicosis.

PICK

Shipley, R. E., and Study, R. S.: Changes in Renal Blood Flow, Extraction of Inulin, Glomerular Filtration Rate, Tissue Pressure and Urine Flow with Acute Alterations of Renal Artery Blood Pressure. Am. J. Physiol. **167:** 676 (Dec.), 1951.

From the perfusion pressures of approximately 20 mm. Hg, renal blood flow, extraction percentage of inulin and glomerular filtration rate increased rapidly up to approximately 80 mm. Hg, above which

all three functions remained relatively constant until perfusion pressure reached approximately 180 mm. Hg. Above this value, RBF increased rapidly, extraction percentage of inulin decreased, while GFR was largely unchanged. Urine flow began at 60 mm. Hg and increased as perfusion pressures mounted.

The authors are of the opinion that a constant RBF and extraction percentage of inulin from 80 to 180 mm. Hg represents autonomous regulation by changes in the afferent arterioles. They suggest that distended renal vessels increase renal tissue pressure and thereby decrease tubular reabsorption of filtrate. This increases urine flow.

OPPENHEIMER

Birath, G., and Crafoord, C.: Function Tests in Pulmonary Surgery. J. Thoracic Surg. **22:** 414 (Oct), 1951.

According to the authors, pulmonary dyspnea has its origin either in the ventilation system, including the air passages and the movements of the diaphragm and chest wall, the pulmonary parenchyma, or the pulmonary circulation. Tests of pulmonary function must therefore deal with these different factors.

Radiologic and fluoroscopic investigation of the costal and diaphragmatic movements is of great value in this respect. Impairment of these movements by intrapleural adhesions has a definite deleterious effect on ventilatory function and is the commonest cause of ventilation insufficiency dyspnea. By using a lead grill with vertical lead bars, registration of the diaphragmatic movements can be obtained.

Spirometric investigation is also of value since it can give information regarding the total lung volume and its subdivisions. This involves estimation of residual capacity as well as of vital capacity. In fact, the former figure may give more pertinent information than the latter. Bronchospirometry is of use in determining function separately in the lung to be subjected to removal and in the normal one. Catheterization of the pulmonary artery is of value in certain cases, particularly if the studies are performed during exercise as well as at rest.

ABRAMSON

PATHOLOGY

Oppenheim, M.: Further Investigations of Myocardosis in Cirrhosis of the Liver. Helvet. med. acta **6:** 573 (Dec.), 1951.

In 47 patients who died from liver cirrhosis with signs of myocardial involvement, anatomic findings, electrocardiograms and blood protein levels were correlated. All cases who died before 50 years of age had hypoproteinemia and abnormal electrocardiograms. All patients who had abnormal electrocardiograms, but normal blood proteins, or vice versa, lived longer than 50 years. No patients with normal electrocardiograms and blood proteins died. A comparison between the degree of anatomic changes in the liver and the alterations of the electrocardiogram pointed to a definite and causal interrelationship.

The author considers these observations a further argument in support of the importance of dysproteinemia in the development of degenerative changes of the myocardium (myocardosis of Wuhrman), found frequently in association with cirrhosis of the liver.

PICK

Hillemans, H. G.: Statistical Investigation on the Frequency of Fatal Pulmonary Embolism in the Post Mortem Material in Freiburg in the Years 1911–1950: Arch. Kreislaufforsch. **17:** 309 (Dec. , 1951.

In an autopsy material of 19,353 cases the author found periodical variations of the incidence of fatal pulmonary embolism, confirmed by statistical methods. Two maxima of frequency were found in the years preceding the two world wars. During the wars, there was a progressive decline and the lowest figures were reached in the years immediately succeeding the two wars. Another increase of pulmonary embolisms occurred after 1924, the years which terminated inflation in Germany, and after 1948, following devaluation of German currency. Thus, the curve of incidence of pulmonary embolism seems to follow changes of economic conditions and of the state of nutrition in the general population.

This was further brought out by evaluation of the material according to body weight, which revealed a greater incidence of the fatal event in persons with increased weight. In the material of 1946 to 1948, the years of the poorest nutrition of the population, weight groups found to have the highest incidence were not represented. In the years of normal conditions of nutrition, there appeared to be a greater tendency to thrombosis and embolism among females than among males, especially when the transition from deficient to normal conditions had occurred rapidly. During the hunger years, the danger of pulmonary embolism was about the same in both sexes.

A slight increase in the absolute number of fatal pulmonary embolisms was noted in the years following the first world war. This is ascribed by the author to an increase of tendency to mobilization of thrombi, possibly in connection with improvement of therapeutic methods and their increased efficiency upon the circulation.

PICK

Martin, J. F., and Bonte, F. J.: Glycogen Disease. Report of Two Cases with Cardiomegaly. Am. J. Roentgenol. **66:** 922 (Dec.), 1951.

The authors describe the clinical, roentgenographic and postmortem findings in two infants with cardiac involvement due to glycogen-storage disease. Both had respiratory distress, one partially due to atelectasis from a compression of a bronchus by a pul-

ronary artery; both had marked cardiac enlargement, one with considerable left ventricular hypertrophy, the degree of hypertrophy in the other being far less striking. No murmurs were noted in either case; left axis deviation was present in one, no electrocardiogram having been obtained in the other. Angiocardiography was performed in one case, demonstrating only slight chamber enlargement, and increased thickness of the left ventricular wall.

The liver was enlarged in one case, not in the other, though both showed the typical staining characteristics on microscopic examination. In both cases, skeletal muscle glycogen content was greatly increased, indicating that the diagnosis could have been established definitely antemortem by muscle biopsy.

SCHWEDEL

Schmid, H. J.: Dissecting Aneurysm of a Coronary Artery. Schweiz. med. Wchnschr. **81:** 1170 (Dec.), 1951.

The author reports a case of bronchial asthma who never had symptoms pointing to coronary disease, and died in a protracted asthmatic attack. Throughout a nine-year period of observation a large mass was noted at repeated x-ray examinations, adjacent to and encroaching upon the anterior aspect of heart shadow, showing partial calcification and only transmitted pulsation. In the electrocardiogram the T wave was deeply inverted in lead I (no precordial leads were obtained). The nature of the mass remained obscure until the post mortem, which revealed a sack-like dissecting aneurysm, measuring 11 cm. in diameter, in the wall of a vessel corresponding to the ramus intermedius of the left coronary artery. The vessel had an anomalous origin directly from the sinus of Valsalva. The wall of this small artery was apparently too weak to bear permanently the full weight of the intra-aortic pressure, which led eventually to a tear in, and subsequent aneurysmatic dilatation of, the vascular structures.

PICK

Hill, W. T., and Reilly, W. A.: Endocardial Fibroelastosis. Am. J. Dis. Child. **82:** 579 (Oct.), 1951.

Endocardial fibroelastosis first described in the latter half of the nineteenth century is a noninflammatory fibrosis of the mural and valvular endocardium. The infants appear normal at birth. The initial symptoms or signs appear suddenly with cyanosis as the most frequent complaint. There may or may not be signs of cardiac enlargement. Congestive heart failure is usual. The cause of death is usually left ventricular failure. Death occurs not more than 10 days after the onset of symptoms. The average age at death is 4 to 6 months.

The authors report a case in which the microscopic findings of the degenerative changes resembled the fibrinoid degeneration seen in the collagen diseases. They studied the alteration with a variety of stains and found a precipitation of the acid mucopolysaccharide ground substance of the connective tissue, the mucinous and homogenous nature of the ground substance, and the proliferation of the connective tissue with an unusual or moderate inflammatory cell reaction. These changes are also thought to be characteristic of the collagen diseases. The authors state that this case strongly suggests that endocardial fibroelastosis be placed in the collagen disease group.

MARGOLIES

PHARMACOLOGY

Mazzella, H.: The Effect of High Doses of Thiamine Upon Circulation. Arch. Internat. pharmacodyn. **86:** 434, 1951.

Fresh solutions of thiamine chloride were injected into the femoral vein of cats, anesthetized with dial, and of chloralosed dogs. On the cat 30 to 50 mg. per kilogram were used while the dogs received 50 to 100 mg. per kilogram. A few minutes after the injection, stimulation of the vagus with strong currents did not cause the usual bradycardia. This effect persisted only for 1 to 2 minutes. Extirpation of the sympathetic trunks did not modify this reaction. The suppression of the vagal cardio-inhibitory effect is assumed to be peripheral. Thiamine inhibits the motor-end plate and ganglionic transmission.

SCHERF

Holzman, D., and Brown, M. G.: The Use of Quinidine in Established Auricular Fibrillation and Flutter. Am. J. M. Sc. **222:** 644 (Dec.), 1951.

The ability of quinidine, as employed by the authors, to reverse auricular fibrillation and flutter to normal sinus rhythm was examined in 57 patients with these arrhythmias. The usual etiologies of heart disease were represented. Congestive failure was present in 36 patients and was under control at the time of quinidine therapy. Gradually increasing doses of the drug were used until the patient received 0.5 Gm. every two hours for seven doses if necessary.

In 30 of the 57 patients, it was possible to restore normal sinus rhythm. Of the 27 failures, 89 per cent had cardial enlargement and 74 per cent had a history of decompensation, whereas these abnormalities were present in 63 per cent and 53 per cent respectively in the successfully treated group. However, it is to be noted that three of the arrhythmias restored to normal sinus rhythm occurred in patients with no heart disease. In this series, fewer of the patients with rheumatic heart disease were restored to sinus rhythm than those with degenerative heart disease.

Petechial hemorrhages and exfoliative dermatitis necessitated discontinuance of therapy in two patients. Symptoms of cinchonism occurred in 49 per cent of the patients but rarely were of sufficient gravity to interfere with the treatment. The electrocardiographic changes attributed to quinidine ther-

apy were: (a) slowing of auricular impulse formation; (b) increase in intraventricular conduction time; (c) increase in auricular conduction time, and (d) evidence of ventricular irritability.

SHUMAN

Stern, P.: The Pharmacology of Recosen: Ztschr. Kreislaufforsch. **40:** 726 (Dec.), 1951.

The author studied the effect of Recosen, a water soluble and protein free extract of the total heart, on normal and damaged hearts of guinea pigs and dogs. Depressed contractility and decreased coronary flow effected by application of pilocarpine or chloral hydrate to isolated hearts of guinea pigs was quickly restored to normal following perfusion by 0.1 cc. of a 1 per cent solution of the extract. Similarly, a cyanotic area produced in the heart of a dog by ligation of a coronary artery disappeared following injection of 1 cc. Recosen into the femoral vein. On the other hand, bronchial contraction and blood pressure elevation produced in dogs by injection of Pilocarpine remained unaffected.

Thus, Recosen appears to have a specific dilating effect on the coronary circulation, possibly related to certain metabolic events in the myocardium, but cannot be considered to be a general spasmolytic agent.

PICK

Carter, M. G.: Cardiac Arrest. J.A.M.A. **147:** 1347 (Dec. 1), 1951.

Cardiac arrest during lobectomy occurred in a man aged 63. After a period of endotrachial aspiration, the patient's color became very dark and the heart came to a complete stop. Cardiac massage was immediately begun by the surgeon, and the anesthetist continued a positive-pressure oxygen insufflation at a regular rate. The operator manually compressed the aorta distal to the take-off of the left subclavian artery. After this maneuver a perceptible pulse was present at both wrists and a blood pressure of about 60 mm. of mercury was noted. Epinephrine (2 cc. 1:1,000) was injected into the left ventricle. Fifteen minutes after the onset, 2 cc. more of epinephrine was injected, 1 cc. into the left ventricular myocardium and 1 cc. into the ventricular chamber.

At this time a few feeble contractions began. Procaine hydrochloride (100 mg.) was given intravenously by the anesthetist in divided doses approximately 10 minutes apart. Cardiac massage was discontinued 25 minutes after the onset of complete cardiac arrest when the heart began with a normal but somewhat weak rhythm. Occlusion of the aorta distal to the subclavian artery was maintained throughout the period of massage and gradually discontinued as the heart began to beat. Resection was abandoned and the thorax was then closed. During the procedure a transfusion of 2000 cc. of blood had been given. The patient was discharged without change in his physical or mental status on the eleventh postoperative day.

The author points out that an adequate cerebral and coronary blood flow was secured by manual occlusion of the aorta distal to the left subclavian artery while cardiac massage was performed. The author suggests this maneuver should be used in all cases of cardiac arrest.

KITCHELL

Krayer, O., Mandoki, J. J., and Mendez, C.: Studies on Veratrum Alkaloids. XVI. The Action of Epinephrine and of Veratramine on the Functional Refractory Period of the Auriculo-ventricular Transmission in the Heart-Lung Preparation of the Dog. J. Pharmacol. & Exper. Therap. **103:** 412 (Dec.), 1951.

It has previously been shown that veratramine antagonizes the accelerator effect of epinephrine on the sinoauricular node of the mammalian heart. In the present study the authors investigated the effects of epinephrine and veratramine on atrioventricular transmission and propagation time in the heart lung preparation of dogs.

Epinephrine shortened the functional and absolutely refractory periods and the A-V propagation time, while veratramine did not have an effect on these properties and was not capable of abolishing or preventing the effect of epinephrine. This investigation thus further indicates the high degree of selectivity of the action of veratramine on the sinoauricular node.

SAGALL

Miller, H., Pollock, R. C., and Griffith, G. C.: Fatal Agranulocytosis Resulting from a Procaine Derivative. J. Lab. & Clin. Med. **38:** 850 (Dec.), 1951.

A case history of fatal agranulocytosis believed due to procaine amide was presented.

Procaine and procaine amide are metabolized in the body by a serum esterase into para-aminobenzoic acid and diethylaminoethanol. Para-aminobenzoic acid has been previously demonstrated to be a direct cause of leukopenia. Aminobenzene derivatives, of which para-aminobenzoic acid is a member, have been repeatedly implicated in the production of fatal and nonfatal agranulocytosis.

It is necessary to presuppose the existence of a previously weakened, damaged or idiosyncratic bone marrow which may be congenital or acquired in the development of agranulocytosis.

It is believed that the incidence of agranulocytosis heretofore was unreported because of the relatively limited dosage of procaine amide employed. It was urged by the authors that when this agent is used, the effects upon the hematopoietic system should be carefully observed.

MINTZ

Leibowitz, S.: Chills and Fever Following Oral Use of Procaine Amide (Pronestyl). New England J. Med. **245:** 1006 (Dec. 27), 1951.

Procaine amide is said to be hydrolyzed only partially, if at all, by plasma esterase to para-aminobenzoic acid and diethylaminoethanol. It consequently has a more prolonged action than procaine hydrochloride and it has been found useful in ventricular arrhythmias and is being employed in some disorders of auricular origin. The toxic effects on oral administration thus far described have been nausea, vomiting, mental confusion and diaphoresis, whereas intravenous use has sometimes been followed by hypotension.

This report concerns a 48 year old man with supraventricular tachycardia for whom procaine amide hydrochloride was prescribed in a dose of 0.5 Gm. four times daily. After one week the patient began to have weakness and sweating during the day and chills and fever each evening. These symptoms cleared when the drug was stopped and recurred within 24 hours when it was begun again. During one of these episodes of chills and fever the rectal temperature was 104 F. but there was no hypotension. Since no other explanation for the febrile reaction could be found, it was attributed to the procaine amide. The patient had received procaine in the course of dental surgery on previous occasions without reactions.

ROSENBAUM

Bakay, L., Selverstone, B., and Sweet, W. H.: Intravascular Distribution of Na^{24} Injected Intravenously in Man. J. Lab. & Clin. Med. **38:** 893 (Dec.), 1951.

Following the intravenous injection of a few cubic centimeters of a solution of $Na^{24}Cl$, the sodium was completely mixed in the major arteries of limbs and head in man in less than a minute.

Marked differences were found in time for the venous concentrations to attain those in the arterial blood. The superficial veins of the feet and legs lag markedly behind those of the limbs unless the individual is vigorously active. Sluggish circulation accompanied by the flow of unlabeled sodium from the extravascular fluid and/or blood pooled in stagnant veins markedly delays mixing. This may be associated either with a motionless state, multiple local thromboses or vasoconstriction.

If the rates of transcapillary exchange of electrolytes are to be studied, it is necessary to obtain many early arterial determinations, because of errors arising from poor mixing. It was suggested that three rather than two rates of exchange of Na^{24} per minute may more nearly describe the processes that occur normally. Such rates of exchange in a motionless, stuporous man were 55 per cent, 9 per cent and 2 per cent, and in a powerfully moving person were 150 per cent, 10 per cent and 0.2 per cent.

MINTZ

Edwards, W. S.: The Effects of Lung Inflation and Epinephrine on Pulmonary Vascular Resistance. Am. J. Physiol. **167:** 756 (Dec.), 1951.

Pulmonary resistance was studied in these experiments in which pressure-flow relationships were determined over wide ranges. Capacity effects on venous flow were controlled by making measurements during periods of static pulmonary inflation or deflation. Small differences in pressure produce large increases in flow. Both positive and negative pressure inflation cause an increase in pulmonary vascular resistance. These conclusions are limited to positive inflation in the open chest. Epinephrine causes a small but definite increase in pulmonary resistance which is independent of elevated venous pressure and cardiac output.

These findings are different from those of others who could not evaluate pressure-flow relations and who did not consider passive resistance changes due to increased pulmonary arterial pressure and flow. Changes in pulmonary arterial pressure and flow produce opposite changes in pulmonary resistance.

OPPENHEIMER

Smith, D. J., and Coxe, J. W.: Reactions of Isolated Pulmonary Blood Vessels to Anoxia, Epinephrine, Acetylcholine, and Histamine. Am. J. Physiol. **167:** 732 (Dec.), 1951.

The authors used an angioplethysmokymographic technic to test the effect of anoxia, epinephrine, acetylcholine, and histamine on isolated pulmonary blood vessels in swine, dogs and cats. Epinephrine caused vasoconstriction of extrapulmonary arteries and veins of the dog, extrapulmonary arteries of the cat, and intrapulmonary arteries of swine. Acetylcholine caused vasoconstriction of the extrapulmonary veins of the dog. Histamine caused constriction of the dog's extrapulmonary veins and the swine's intrapulmonary veins. A small number of human arteries and veins were constricted by both epinephrine and histamine. The absence of oxygen did not significantly change any of these responses.

OPPENHEIMER

McCubbin, J. W., and Page, I. H.: Effect of Veratramine on Arterial Pressure and Heart Rate in Normal and Hypertensive Dogs. Am. J. Physiol. **167:** 714 (Dec.), 1951.

Veratramine, on intravenous administration, decreased slightly to moderately the blood pressure of normal and renal hypertensive dogs. In neurogenic hypertensive dogs veratramine produces a marked hypotension. This effect persisted when cardiac slowing was prevented by sympathectomy. In the absence of slowing veratramine caused hypotension with increased minute and stroke volumes. This indicates a decrease in total peripheral resistance. Autonomic blockade with tetraethylammonium chloride and sympathectomy in neurogenic hypertensive dogs reduces the hypotensive response to veratra-

mine. Veratramine causes a further decrease when given during tetraethylammonium chloride hypotension. Veratramine does not potentiate adrenaline and noradrenaline. Carotid sinus reflexes are unchanged after veratramine. Neither atropine nor bilateral vagotomy alters veratramine effects.

The authors conclude that veratramine lowers pressure mainly by decreasing peripheral resistance. This action is independent of changes in heart rate and output. The increased effect in neurogenic hypertensive dogs may represent inhibition of increased vasomotor activity.

OPPENHEIMER

Lu, G.: The Mechanism of the Vasomotor Action of Quinidine. J. Pharmacol. & Exper. Therap. **103:** 441 (Dec.), 1951.

The intravenous administration of quinidine sulfate in dogs and cats resulted in a fall of blood pressure accompanied by a marked increase in leg and a decrease in kidney and spleen volumes. The cardiac output, however, was unchanged. Studies on the mechanism of this peripheral dilatation indicated that quinidine did not produce any depression of the vasomotor centers centrally but acted mainly as a depressor of the sympathetic receptors and partially as a direct depressor of vascular smooth muscle.

SAGALL

Berger, H.: Thrombopenic Purpura Following Use of Digitoxin. J.A.M.A. **148:** 282 (Jan. 26), 1952.

The author reports a case of thrombopenic purpura which developed in a patient with rheumatic heart disease. It became apparent that digitoxin was the offending medicament when it was inadvertently given to her without changing any of the other drugs being given. Later the administration of other drugs given prior to development of the purpuric state failed to initiate any evidence of the blood dyscrasia. Small doses of digitoxin were given again and the daily blood cell count showed a decrease in platelets on the sixth day. It appears that digitoxin is capable, though rarely, of producing thrombopenic purpura.

KITCHELL

Johnson, S. A. M., and Meyer, O. O.: The Treatment of Lupus Erythematosus Disseminatus with Cortisone. Am. J. M. Sc. **223:** 9 (Jan.), 1952.

Improvement in the signs and symptoms of lupus erythematosus occurred in nine cases treated with cortisone acetate. The patients received 6 Gm. of the drug, either on a continuous schedule or in several courses with rest intervals. Upon discontinuance of therapy, the remission was not sustained in any instance.

Cortisone, in several of the seriously ill patients, was apparently effective in tiding patients over acute pericarditic and cardiac complications. The usual precautions of limiting the sodium intake and of adding 3 Gm. of potassium chloride daily were followed to avoid some of the complications of such therapy; hirsutism, acne and thinning of the hair were noted. Ascites occurred in one patient while a toxic psychosis was precipitated in another.

The authors noted an increase in the leukocyte counts in some patients; however, a complete disappearance of lupus erythematosus cells from the bone marrow was not uniformly observed. Several patients in this group had previously received para-aminobenzoic acid with some improvement which was not sustained and less rapid than that obtained with cortisone.

SHUMAN

Chapman, D. W., Skaggs, R. H., Thomas, J. R., and Greene, J. A.: The Effect of Cortisone in Experimental Myocardial Infarction. Am. J. M. Sc. **223:** 41 (Jan.), 1952.

Myocardial infarction was produced by ligation of the left anterior descending coronary artery of dogs, following which cortisone was administered for 10 day intervals. Infarctions were produced in another group which received no cortisone treatment. The adequacy of cortisone therapy was evaluated by means of eosinophile counts. These showed a persistent fall in the treated group, whereas the counts returned to normal following recovery from operation in the control animals.

The result of this study indicated that cortisone had no deleterious effect upon the infarction, either from the standpoint of size of the lesion or its rate of healing. No electrolyte disturbances were noted in these experiments. There was slight evidence of adrenal cortical atrophy after 10 days of cortisone therapy; however, 20 days after cessation of cortisone therapy the adrenals were normal. Therefore, it would appear that cortisone is not contraindicated in the presence of myocardial infarction in dogs.

SHUMAN

Assali, N. S., and Rosenkrantz, J. G.: Studies on Autonomic Blockade. V. The Inhibition of Water Diuresis by High Spinal Anesthesia in the Pregnant Woman. Surg., Gynec. & Obst. **93:** 468 (Oct.), 1951.

Spinal anesthesia has been advocated in the treatment of toxemia of pregnancy on the basis that it reduces the blood pressure and increases urinary output. Results from prior experiments by the authors had cast doubt on this hypothesis. Therefore they tested the effect of high spinal anesthesia on water induced diuresis in 11 normotensive pregnant patients and in eight patients with a toxemia of pregnancy.

Following high spinal anesthesia the changes in blood pressure were variable; some patients had a marked fall, some a minimal and some none.

The control urine flow in both the normotensives and the toxemic patients was variable; but the rate of urine flow of the toxemic patients was consistently

lower than that of the normotensives even though the intake was the same. Following the high spinal anesthesia, the urine flow was markedly lowered in all patients except one normotensive. The greatest reduction in flow was manifested by the normotensive group.

The oliguria usually coincided with the hypotension, but in some cases it occurred without any marked change in the blood pressure. The duration of oliguria always outlasted the blood pressure fall. In one case the blood pressure was restored to control level with ephedrine, and the oliguria persisted.

The inhibition of water diuresis may be due to one or a combination of three factors: (a) fall in blood pressure and cardiac output with decreased effective renal blood flow, filtration pressure, and filtration rate; (b) compensatory renal vasoconstriction secondary to (a); and (c) stimulation of secretion of the hormone Pitressin.

The results of this investigation do not support the concept that spinal anesthesia increases the urine flow in patients with a toxemia of pregnancy.

FROBESE

Duchene-Marullaz, P.: On the Mechanism of Cardioacceleration Produced by Atropine. Compt. rend. Soc. Biol. **145:** 1334 (Sept.), 1951.

The authors have demonstrated the absence of a permanent cardiodepressor (vagal) tone in the rabbit's heart. This time, they investigated the mechanism of atropine action and the possibility of a direct accelerating effect of the drug on the rabbit's heart. In a series of experiments, the dose of atropine injected in unanesthetized animals was progressively increased to 9 mg. The heart rate varied only within limits of physiologic fluctuations so that, for this species, a direct effect of the drug could be ruled out.

However, the conditions are different in man. The doses used in the usual "atropine test" are insufficient to abolish completely all inhibitory effects of the vagus on the heart. Excessively high heart rates in man following administration of atropine may be due to individual variations in the tone of the accelerans, as well as to some unknown action of the belladonna alkaloid upon cardiac rhythm, which may be independent of its vagolytic effect.

PICK

PHYSIOLOGY

Kaneko, Y.: Studies on the Peripheral Blood Volume in the Skin. Shikoku acta med. **2:** 7 (Dec.), 1951.

The peripheral blood volume increased with a small dose of histamine (0.001 to 0.04 mg. per kilogram), but decreased with a large dose (0.05 mg. per kilogram). The peripheral blood volume decreased with a small dose (1.5 to 3.0 mg. per kilogram) but increased with a large dose (6.0 mg. per kilogram) of restamine. The rival action of both drugs is more remarkable by mixed injection, and 0.01 mg. of histamine matches 3.0 mg. of restamine.

BERNSTEIN

Deane, N.: Intracellular Water in Man. J. Clin. Investigation **30:** 1469 (Dec.), 1951.

The simultaneous measurements of total body water and extracellular fluid in 11 male subjects are presented. Total body water was determined as the volume of distribution of antipyrine. Extracellular fluid was measured by the maximal volume of distribution of sucrose as determined by the calibrated infusion technique. Intracellular water was calculated as a difference between total body water and extracellular fluid.

Intracellular water averages 40.6 per cent of body weight (with a range of from 34.7 to 48.0). Intracellular water formed 70 per cent of total body water and 50 per cent of cellular mass.

WAIFE

RHEUMATIC FEVER

Stetson, C. A., Jr.: The Occurrence of Leukocyte-Platelet Thrombosis in Rheumatic Carditis. J. Exper. Med. **94:** 493 (Dec. 1), 1951.

Microscopic sections of cardiac tissue of patients dying with active rheumatic fever and rheumatic carditis revealed leukocyte-platelet thrombosis of capillaries and small veins. The thrombi were seen most frequently in the myocardial and pericardial vessels and less commonly in the subendocardium in the adventitia of the aorta and in valves. The thrombi were not found in the larger branches of the coronary arteries and veins.

A consistent correlation was found between the occurrence of these vascular lesions and the presence of Aschoff bodies. Since leukocyte-platelet thrombosis has been shown to play a major role in the production of the extensive tissue damage observed during the course of the Arthus and Shwartzman phenomena, the author suggests that these thrombi may be of significance in the pathogenesis of rheumatic carditis.

SAGALL

ROENTGENOLOGY

Johnson, H. C., and Walker, A. E.: The Angiographic Diagnosis of Spontaneous Thrombosis of the Internal and Common Carotid Arteries. J. Neurosurgery **8:** 631 (Nov.), 1951.

During the course of over 500 cerebral angiograms for brain tumor or cerebral aneurysm suspects, the authors encountered six cases in which spontaneous thrombosis of the internal carotid artery was diagnosed. In reviewing the literature, they were able to find 101 cases of spontaneous carotid thrombosis which had been diagnosed by angiography. The significant features of the clinical course, etiology, treatment, and angiographic characteristics of the 107 cases are summarized.

The onset of the illness falls in one of three types: (1) 35 per cent of the patients had a sudden apoplectic or catastrophic type of onset with rapid loss of consciousness, hemiplegia, or severe headache; (2) 25 per cent of the patients had a slowly progressive onset with severe headaches over a period of months, sporadic convulsive seizures, paresthesias, and weaknesses which increased suddenly in severity just prior to medical aid; (3) the remaining 40 per cent had transient attacks of headache, hemiparesis paresthesias, and aphasias.

No single etiologic factor could be implicated, but the two most common ones seemed to be arteriosclerosis and thromboangiitis obliterans. Most patients had no specific treatment and the prognosis was generally poor.

In 97 of the cases the radiopaque dye filled only the external carotid vessels and thrombotic block of the internal carotid was noted by angiography. In six cases the common, external, and internal carotid arteries were found to be thrombosed in the neck when they were exposed for injection. In four cases the occlusion was bilateral. Occasionally one can demonstrate the anterior communicating and anterior cerebral arteries of the occluded side by performing angiography on the normal side. This is not without hazard, as death has followed angiography performed on the side opposite an occluded internal carotid artery.

The authors feel that without the use of cerebral angiography, a large number of these lesions would have been incorrectly diagnosed as brain tumors or cerebral aneurysms.

FROBESE

Anderson, P. T., Anderson, I., Eltorm, H., Poulsen, T., Glistrup, E. and Petersen, H.: Angiopulmography. Acta radiol. **36:** 257 (Oct.), 1951.

The authors discuss the application of contrast opacification of the major arteries and veins of the lungs to the diagnosis of various pulmonary conditions. Space displacement, constriction, compression and occlusion of arteries and veins led to diagnoses of tumor, substantiated at operation as malignant or metastatic carcinomata, tuberculoma, and in one instance a dermoid cyst. The authors suggest that the pattern of vascularization of a tumor mass may be suggestive though not diagnostic of a malignancy. In other instances, the great vessels were unaffected, and the procedure of angiopulmography did not materially aid in the diagnosis.

SCHWEDEL

Raphael, R. L., Schnabel, T. G., Jr., and Leopold, S. S.: A New Method for Demonstrating an Aberrant Right Subclavian Artery. Radiology **58:** 89 (Jan.), 1952.

The right brachial artery is punctured with a no. 19 special thin walled needle through which a radiopaque catheter 70 cm. in length is inserted and directed under fluoroscopic control through the brachial, axillary and subclavian arteries to the aorta. Fluoroscopy and roentgenograms with the catheter in place within the lumen of the vessel demonstrate the actual course of the subclavian artery and its entrance into the aorta. These may be done in conjunction with the usual method of demonstrating this congenital anomaly on a barium filled esophagus.

SCHWEDEL

Shapiro, R.: Thrombosis of the Internal Carotid Artery. Radiology. **58:** 94 (Jan.), 1952.

The authors describe the clinical and roentgenographic findings in three cases of thrombosis of the internal carotid artery, one associated with an arteriovenous aneurysm of the intracranial portion, clinically evidenced by weakness and paralysis. The diagnosis was indicated on arteriography.

SCHWEDEL

Honig, E. I., Steinberg, I., and Dotter, C. D.: Innominate Artery: Angiocardiographic Study. Radiology **58:** 80 (Jan.), 1952.

In a review of 80 angiocardiograms of individuals with hypertensive or arteriosclerotic disease, buckling of the innominate artery was demonstrable in seven, to the right in five, to the left in the other two. In six others dilatation was present without buckling.

One hundred forty-one cases of syphilitic aortitis were also reviewed. Fifty-seven of these (39 per cent) had aneurysms of the aorta or brachiocephalic vessels; 12 had innominate artery aneurysms, one half of the fusiform type, the other half of the saccular type. The symptoms of innominate artery aneurysm were: dyspnea, dysphagia, hoarseness, cough, and weight loss; one had circulatory disturbances in the right arm, another had a Horner's syndrome, three had unilateral clubbing of the fingers.

Eleven of 37 cases of coarctation of the aorta showed dilatation and tortuosity of the innominate on angiocardiography. The authors also discuss the role of this diagnostic procedure in left-sided origin of the innominate artery, and in aberrant right subclavian artery origin. They stress that angiocardiography facilitates the differential diagnosis between dilatation, aneurysm, substernal thyroid, and right aortic arch with the descending portion on the left side and an aortic diverticulum on the right simulating a normal left sided aortic knob.

SCHWEDEL

SURGERY IN HEART AND VASCULAR SYSTEM

Shumacker, H. B., Jr.: Use of the Subclavian Artery in the Surgical Treatment of Coarctation of the Aorta. Surg., Gynec., & Obst. **93:** 491 (Oct.), 1951.

End-to-end aortic anastomosis is the most satisfactory method in the surgical correction of coarcta

tion of the aorta. Occasionally this procedure is not possible for technical reasons, and an alternative method must be carried out. Transplantation of preserved segments of homologous aorta may be used. Gross has reported good results with this method, but it is known that these vascular transplants may be destroyed and replaced by the host. Whether they will function indefinitely is not known. In certain instances it is possible to bridge the gap with the subclavian artery in an end-to-end subclavian-aortic anastomosis. These have been only moderately successful. The author feels that failure may result in these cases when the subclavian is divided and turned down to reach the distal aortic stump, as it may buckle or thrombose and impede the flow of blood.

Instead, he advocates using the inferior aspect of the depressed subclavian artery for the anastomosis and closing the divided end as a blind stump. Or one can use the subclavian as a free vessel graft between the inferior aspect of the aortic arch at the level of the origin of the left common carotid and the inferior aortic stump. Either of these methods prevent angulation of the divided subclavian artery.

Four cases are reviewed. In two correction of the defect was done by the method recommended here with good result.

FROBESE

Keefer, E. B. C., Glenn, F., and Dotter, C. T.: Resection and End-to-end Anastomosis of the Thoracic Aorta in Puppies; Two and Three-quarter Year Follow-up. Ann. Surg. **134:** 969 (Dec.), 1951.

The authors performed end-to-end anastomosis of the thoracic aorta in seven puppies, and followed the animals for several years. They wanted to determine whether a situation comparable to coarctation of the aorta could be produced. This definitely occurred in one animal and was less marked in another. The changes consisted of hypertension, clinical symptoms, and roentgenographic findings related to coarctation of the thoracic aorta.

Since the alterations did not take place in the other animals, it was believed that in them the anastomotic area of the aorta probably increased in caliber, although not at the same pace as the growth of the adjacent portions. Because of the changes observed in the series, it was concluded that earlier correction of coarctation of the aorta in human patients is desirable even though a second procedure will be necessary in certain cases.

ABRAMSON

Kay, J. H.: The Treatment of Cardiac Arrest. An Experimental Study. Surg., Gynec. & Obst. **93:** 682 (Dec.), 1951.

Cardiac arrest may occur as ventricular standstill or as ventricular fibrillation. When it occurs during a surgical procedure, one has several minutes in which to institute therapy, and this treatment must be the proper one for success. Various forms of treatment have been recommended; this study was done to determine the most satisfactory.

The author produced and successfully treated cardiac arrest 205 times in 72 dogs. Ventricular standstill was produced by deep anesthesia and ventricular fibrillation was produced by electrical stimulation.

Cardiac massage was found to be the most important therapeutic measure. An effective and practical rate of manual cardiac compression was found to be between 35 and 50 per minute.

In ventricular standstill, one to two minutes of massage started many of the hearts. Others needed the injection of one of the cardiac stimulants. If the stimulant was injected prior to massage, fibrillation often ensued. It was necessary to massage the heart to circulate the injection to the myocardium. Best results were obtained by injecting the stimulant into the left ventricle, as it reached the myocardium faster, and the puncture site did not bleed as did a similar wound in the auricle.

The stimulants tested were, in the order of effectiveness: epinephrine, calcium chloride, barium chloride, and isopropylepinephrine. The amount of epinephrine used was 0.1 cc. of a 1:1000 solution. When as much as 1 cc. was used, 30 per cent of the hearts went into ventricular fibrillation.

Ventricular fibrillation was best treated by massage until the heart was no longer dilated and cyanotic; then single or serial electric shocks were applied directly to the heart. The injection of procaine was necessary for success in only one instance of 190 fibrillations. In 12 instances procaine was used with electrical defibrillation and appeared to make the ventricular standstill that follows more refractory to treatment by massage. The author was unable to stop fibrillation in any of 35 attempts by the injection of procaine and cardiac massage without electrical stimulation. Therefore, he concludes that procaine is not a satisfactory drug for the treatment of cardiac arrest.

FROBESE

VASCULAR DISEASE

Brown, R. A.: Polycystic Disease of The Kidneys And Intra-Cranial Aneurysms. Glasgow M. J. **32:** 333 (Dec.), 1951.

Six cases of polycystic kidney associated with intracranial aneurysm were found in 11,245 autopsies. The relationship was present in four per cent of cases of aneurysm and 16.6 per cent of cases of polycystic kidney, while 22.2 per cent of cases of polycystic kidney died from subarachnoid hemorrhage. It is concluded that polycystic kidneys and intracranial aneurysms are associated more frequently than would occur by chance. Although hypertension and vascular degeneration may play some part in the development of the aneurysms, it

is more probable that there is a common etiology and therefore support is given to the congenital origin of both intracranial aneurysms and the adult type of polycystic disease.

Although coarctation of the aorta is more widely known as an associated finding with intracranial aneurysms, the association with polycystic disease appears to be more common. Subarachnoid hemorrhage, frequently from ruptured aneurysm, is a not uncommon cause of death in polycystic disease.

BERNSTEIN

Texter, E. C., Jr., Redisch, W., and Steele, J. M.: Induced Intermittent Claudication. Am. J. M. Sc. **222:** 653 (Dec.), 1951.

A friction belt bicycle ergometer was employed to study the use of this apparatus as a method of producing claudication symptoms in patients with arteriosclerosis of the lower extremity vessels. Three groups of patients were included; group 1, with no evidence of arteriosclerosis; group 2, with cardiorenal, or cerebral sclerosis but no clinical peripheral sclerosis as determined by x-rays and oscillometric studies; and group 3, with signs and symptoms of obliterating arteriosclerosis of the peripheral vessels.

The exercise test did not produce claudication pain in the first or second groups; however, in the third group, all patients manifested symptoms of arterial insufficiency. It was felt that the test described was no better than a good history and clinical examination in the diagnosis of peripheral arteriosclerosis obliterans.

SHUMAN

Domzalski, C. A.: Diagnosis of Dissecting Aneurysm of the Aorta. Arch. Int. Med. **88:** 770 (Dec.), 1951.

The clinical and pathologic features of nine cases of dissecting aneurysm of the aorta are reviewed. The autopsy incidence was one in 99, higher than in any previous series. All but one of the patients were over 40 years of age; all but one were men, and all but one had arteriosclerosis. All but one had hypertension, and all but one died within eight days of onset.

The dominant clinical features suggested cardiac disease in three, neurologic disease in two, abdominal disease in two, and pulmonary disease in one. One patient had a healed "silent" dissecting aneurysm. Basal heart murmurs, stressed by others as a diagnostic aid, were not encountered. Four patients had leukocytosis, the white cell count exceeding 20,000, and three showed rapid development of anemia. Two had hematuria, one gross and the other microscopic. Chest roentgenograms in three cases showed significant abnormalities. Electrocardiograms in three patients served to rule out myocardial infarction initially. A second electrocardiogram in one case disclosed a coronary occlusion which was caused by the aortic dissection.

At autopsy, dissection was extensive in six patients and small in three. In two patients no intimal tear could be found. Hemopericardium was observed in three patients and left hemothorax in three. Idiopathic cystic medionecrosis was seen in five cases. Other clinical conditions known to be associated with a high incidence of dissecting aneurysm, such as coarctation of the aorta, Marfan's syndrome (arachnodactyly), and pregnancy, were not encountered in this series.

BERNSTEIN

Leonard, F. C., and Vassos, G. A., Jr.: Congenital Arteriovenous Fistulation of the Lower Limb: Report of Case Successfully Treated by Total Excision, New England J. Med. **245:** 885 (Dec. 6), 1951.

The authors report the eightieth case of fistulation of the lower limb to be recorded in the literature and the fifth to be managed successfully by total resection. It is emphasized that congenital arteriovenous shunts are always multiple in contrast to those of traumatic origin, and for that reason the term *fistulation* is considered more appropriate in these cases than *fistula*.

In the case at hand, it was possible to excise the masses of anomalous vessels, which included some 40 communications over a 25 cm. segment of main vessels through separate iliac and thigh incisions, while preserving the main-artery continuity. If this continuity cannot be preserved, reconstruction by venous or arterial grafts will usually be necessary to preserve the involved limb.

ROSENBAUM

Adson, A. W.: Control of Recurring Hemiparesis by Bilateral Removal of the Superior Cervical Sympathetic Ganglia: Report of Two Cases, Proc. Staff. Meet., Mayo Clin. **26:** 518 (Dec.), 1951.

The authors report two recent experiences in the management of recurrent transitory hemiparesis by bilateral removal of the superior cervical sympathetic ganglia. Both patients were suffering from hypertension, and both patients had had attacks of transitory hemiparesis. The transitory nature of the hemiparesis suggested that the attacks were the result of angiospasm of either the internal carotid artery or the middle cerebral artery.

The author is more inclined to believe that the angiospasm occurred in the internal carotid artery, since relief was obtained by interrupting vasomotor fibers and removing the superior cervical sympathetic ganglia. This opinion is further substantiated by observations made in the course of the ligations of the internal carotid artery for aneurysms. The mere handling of the artery will cause it to go into spasm

and shrink to a fourth its normal size; but if 0.5 per cent solution of Metycaine is injected into the adventitious coat, no vascular spasm takes place during ligation of the internal carotid artery.

SIMON

OTHER SUBJECTS

Dresdale, D. T., Schultz, M., and Michtom, R. J.: Primary Pulmonary Hypertension. Am. J. Med. **11:** 686 (Dec.), 1951.

In primary pulmonary hypertension an elevated pulmonary artery pressure exists without demonstrable cause. The authors report the clinical and hemodynamic factors elicited in three patients with this condition. The salient clinical features are exertional weakness and dyspnea in patients who subsequently develop right heart failure without antecedent cardiac or pulmonary disease. Effort syncope and angina are most significant when present. Sudden death is not infrequent.

The pertinent physical findings are a normal systemic blood pressure, clear lungs, an accentuated pulmonic second sound, and the variability or absence of heart murmurs. The electrocardiographic tracings are consistent with right ventricular hypertrophy. The characteristic x-ray findings are right ventricular enlargement, a bulging pulmonary artery segment, prominent hilar vessels, and normal or diminished intrapulmonary vascular markings. Cardiac catheterization revealed greatly elevated pulmonary artery pressures, elevated right ventricular end diastolic pressures, diminished cardiac outputs, increased arteriovenous oxygen differences, and normal arterial blood oxygen saturations. A seven to ninefold increase in pulmonary resistance was calculated at rest.

The authors support the view that the locus of increased resistance is in the small, pulmonary arteries. Isolated overactivity of the sympathetic nervous system was suggested by the pronounced effect of priscoline in lowering the pulmonary artery blood pressure. The problem of sympathectomy in primary pulmonary hypertension is raised.

HARRIS

Wells, J. S., and Brown, P.: Cor Pulmonale Resulting from Pulmonary Arteriosclerosis. Am. J. Roentgenol. **66:** 894 (Dec.), 1951.

The authors report a case of progressive dyspnea of several years' duration. In the later stages, it became associated with the development of a loud systolic murmur and accentuation of the second sound in the pulmonic area, and, on roentgenography, an increasing prominence of the pulmonary artery segment and its hilar branches, then evident cardiac enlargement and right hydrothorax. Edema developed two weeks prior to her death.

Postmortem examination revealed right ventricular and atrial enlargement, pulmonary artery atheromatosis and dilatation, and a pronounced hypertrophy of the medial coat of the medium and small sized branches of the pulmonary artery. There was no intracardiac lesion or lung disease present which might have accounted for the pulmonary arteriosclerosis.

SCHWEDEL

Cudkowicz, L., and Armstrong, J. B.: Observations on the Normal Anatomy of the Bronchial Arteries. Thorax **6:** 343 (Dec.), 1951.

The bronchial arteries in 10 normal lungs were injected with a radiopaque medium and studied radiologically and histologically. The territory of the bronchial arteries was found to extend to all lung structures with the exception only of the epithelium of the pulmonary capillaries. No precapillary anastomoses between the pulmonary and bronchial arteries were found in normal human lungs. A constant radiographic pattern for the bronchial arteries in normal lungs was demonstrated.

The histologic examination of the intrapulmonary distribution of the bronchial arteries indicated that the supporting framework of the alveoli receives its own independent arterial blood supply from vessels of the interlobular septa, which reach the air sacs at right angles to the alveolar ducts.

BERNSTEIN

BOOKS RECEIVED

CIRCULATION is very glad to acknowledge the receipt of the following books. Insofar as space permits, as many appropriate books as possible will be reviewed.

Fainting. Physiological and Psychological Considerations. *George L. Engel, M.D., Associate Professor of Medicine and Psychiatry, University of Rochester, School of Medicine and Dentistry, Rochester.* Springfield, Ill., Charles C Thomas, 1950. 141 pages, 4 figures. American Lectures in Neurology. $2.75.

Twentieth Anniversary Review of the Josiah Macy, Jr. Foundation. New York, Josiah Macy, Jr. Foundation, 1950. 110 pages.

Notions Cardiologiques Nouvelles. *C. Lian and P. Danset.* Paris, Masson et Cie, 1951. 214 pages, 39 figures. 800 fr.

Herzshalldiagnastick in Klinik und Praxis. Eine Einführung in den Praktischen Gebrauch der Herzshallschreibung. *Jörgen Schmidt-Voigt, M.D.* Stuttgart, Georg Thieme, 1951. 116 pages, 33 figures, 1 table. DM 9.60.

The Kidney—Structure and Function in Health, and Disease. *Homer W. Smith, A.B., Sc.D. M.S., Professor of Physiology, New York University, College of Medicine, N. Y.* New York, Oxford University Press, 1951. 1,049 pages, 153 figures, 18 tables. $12.50.

Industrial Health and Medical Programs. *Compiled by Margaret C. Klem, Margaret F. McKiever and Walter Lear, M.D.* Public Health Service Publication no. 15. Washington, D. C., Federal Security Agency, 1951. 397 pages.

Low-Sodium Diet—A Manual for the Patient. *Thurman B. Rice, A.M., M.D., Professor of Public Health, Indiana University School of Medicine, Indianapolis.* Philadelphia, Lea & Febiger, 1951. 103 pages, 14 charts. $2.75.

The Quantitation of Mixtures of Hemoglobin Derivatives by Photoelectric Spectrophotometry. *Francis T. Hunter, A.M., M.D., Association Medicine, Harvard Medical School; Associate Physician and Clinical Pathologist, Massachusetts General Hospital, Boston.* Springfield, Ill., Charles C Thomas, 1951. 226 pages, 42 charts, 6 figures. $8.00.

A Color Atlas of Morphologic Hematology with a Guide to Clinical Interpretation. *Geneva A. Daland, B. S., Chief Laboratory Assistant in Hematology, Thorndike Memorial Hospital; Research Laboratory Technician, Boston City Hospital. Edited by Thomas Hale Ham, M.D., Assistant Professor of Medicine, Harvard Medical School; Associate Director, Thorndike Memorial Laboratory; Junior Visiting Physician, Boston City Hospital.* Cambridge, Mass., Harvard University Press, 1951. 74 pages, 15 plates, 12 tables. Illustrations by Ella Piotti. $5.00.

Clinical Hematology. *Maxwell M. Wintrobe, M.D. Ph.D., Professor of Medicine, Director of Laboratory for Study of Hereditary and Metabolic Disorders, University of Utah, College of Medicine, Salt Lake City, Utah.* Third edition. Philadelphia, Lea & Febiger, 1951. 1,048 pages, 220 figures, 17 plates, 13 in color. $12.50.

The Architecture of Normal and Malformed Hearts. Phylogenetic Theory of Their Development. *Alexander Spitzer, M.D., Late Professor of Anatomy, University of Vienna. With a summary and analysis of the theory by Maurice Lev, B.S., M.D., Associate Professor of Pathology, University of Illinois College of Medicine; Associate Pathologist, University of Illinois Hospitals, Chicago., and Aloysius Vass, M.D. With a Foreword by Otto Saphir, M.D., Pathologist, Michael Reese Hospital, Chicago.* Springfield, Ill., Charles C Thomas, 1951. 176 pages, 50 figures. $5.00.

Grouping, Typing and Banking of Blood. *Otakar Jaroslav Pollak, M.D., Ph.D., Director Blood Bank; Chief, Department of Anatomical, Clinical and Experimental Pathology, and Director, School of Medical Technologists, Quincy City Hospital, Quincy, Mass.; Consulting Pathologist, Jordan Hospital, Plymouth, Mass.* Springfield, Ill., Charles C Thomas, 1951. 163 pages, 50 tables, 25 figures. $5.75.

Angiocardiography. Annals of Roentgenology. Volume XX. *Charles T. Dotter, M.D., Associate Professor of Radiology, Cornell University Medical College; Assistant Attending Radiologist, New York Hospital, and Israel Steinberg, M.D., Assistant Clinical Professor of Radiology and Medicine, Cornell University Medical College; Assistant Attending Radiologist and Physician to Outpatients, New York Hospital; Attending Physicians and Chief of Chest Clinic, Sydenham Hospital; Attending Consultant, Chest Diseases, V. A. Hospital, Bronx; Consultant, Angiocardiography, U. S. Naval Hospital, St. Albans, New York.* New York, Paul B. Hoeber, 1951. 304 pages, 252 figures (635 illustrations). $16.00.

Thyroid Function and Its Possible Role in Vascular Degeneration. *William B. Kountz, M.D., Assistant Professor of Clinical Medicine, Washington University School of Medicine; Director, Clinical Services, Division of Gerontology, Wash. Univer-*

sity School of Medicine and St. Louis City Infirmary Hospital; Consulting Physician, Barnes Hospital and Lutheran Hospital, St. Louis. Springfield, Ill., Charles C Thomas, 1951. 62 pages, 10 figures. American Lectures in Circulation, no. 108. $2.25.

An Atlas of Normal Radiographic Anatomy. *Isadore Meschan, M.A., M.D., Professor and Head of Department of Radiology, University of Arkansas, School of Medicine, with assistance of R. M. F. Farrer-Meschan, M.B., B.S., Melbourne, Australia.* Philadelphia, W. B. Saunders, 1951. 593 pages, 362 figures.

The Normal Cerebral Angiogram. *Arthur Ecker M.D., Ph.D., Surgical Neurologist, Syracuse, N. Y.* Springfield, Ill., Charles C Thomas., 1951. 190 pages, 140 figures. $6.50.

Kymographiscke Rontgendiagnosik zur Beusteilung des Herzens in Beisplielen. *Prof. Dr. Pleikart Stumpf, Munchen.* Stuttgart, Georg Thieme, 1951. 120 pages, 164 figures, 2 tables. DM 25.50.

Medizinische Rontgentechnik. I. Skelettaufnahmen und Organuntersuchunzen. *Prof. Dr. Med. Herbert Schoen, Karlsruhe.* Stuttgart, Georg Theime, 1951. 228 pages, 476 figures. DM 22.50.

Man and His Years. An Account of the First National Conference in Aging. *Sponsored by the Federal Security Agency.* Raleigh, N. C., Health Publications Institute, Inc., 1951. 311 pages.

Cardiac Pain. *Seymour H. Rinzler, M.D., Adjunct in Medicine and Cardiovascular Research Unit, Beth Israel Hospital; Instructor in Rehabilitation, New York University College of Medicine; Associate Visiting Physician, Bellevue Hospital, New York.* Springfield, Ill., Charles C Thomas, 1951. 139 pages 3 tables, 6 figures. $3.75.

Physical Medicine and Rehabilitation for the Aged. *Walter S. McClellan, M.D., Medical Director; The Saratoga Spa, Saratoga Springs, New York; Associate Professor of Medicine, Albany Medical College, Albany.* Springfield, Ill., Charles C Thomas, 1951. 81 pages, 9 figures. American Lectures in Physical Medicine, No. 105. $2.00.

Electrocardiographic Studies in Normal Infants and Children. *Robert F. Ziegler, M.D., Associate in Cardiology in Charge of Section of Pediatrics Cardiology, Henry Ford Hospital, Detroit.* Springfield, Ill., Charles C Thomas., 1951. 207 pages, 297 illustrations, 33 tables. $10.50.

Roentgenology of the Heart and Great Vessels. *Harry E. Underleider, M.D., and Richard Gubner, M.D., Equitable Life Assurance Society of the U.S. Reprinted from W. D. Stroud's "Diagnosis and Treatment of Cardiovascular Disease."* Third Edition. Philadelphia, F. A. Davis, 1950. 109 pages, 102 figures.

Observations on the General Effects of Injury in Man with Special Reference to Wound Shock. *R. T. Grant and E. B. Reeve, from Clinical Research Unit of Medical Research Council, Guy's Hospital, London.* London, Medical Research Council Special Report Series #277, Privy Council, His Majesty's Stationery Office, 1951. 314 pages, 51 tables 19 figures. 8 s 6 d net.

Kreislaufuntersuchungen am Menschen mit Fortlaufend Registreirenden Methoden. Prof. Dr. *K. Matthes,* Erlangen. Stuttgart, Georg Thieme, 1951. 326 pages, 205 figures, 10 tables. DM 48.

Benzoato (3) de Estrofantidina. Acao Cardiovascular e Valor Terapeutico. *Dr. Eduardo Zaccaro Faraco.* Porto Alegre, Brazil, Oficinas Graficas da Livraria do Globo, 1950. 313 pages, 111 figures, 16 tables.

Modern Electrocardiography. Volume I. The P-Q-R-S-T-U- Complex. *Eugene Lepeschkin, M.D., Assistant Professor of Experimental Medicine, University of Vermont, College of Medicine. Foreword by Frank N. Wilson, M.D., Professor of Medicine, University of Michigan Medical School.* Baltimore, Williams & Wilkins, 1951. 598 pages, 91 figures, 26 tables. $12.00.

Klinische Elektrokardiographie. Lehrbuch fur Studierende und Arzte. *Dr. Max Holzmann, Zurich.* Stuttgart, Georg Thieme, 1952. 652 pages, 302 figures, 9 tables. DM 69.50.

Urine and the Urinary Sediment. A Practical Manual and Atlas. *Richard W. Lipman, B.S., M.D., Research Associate, Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles; Fellow of the John Simon Guggenheim Memorial Foundation.* Springfield, Ill., Charles C Thomas, 1952. 124 pages, 61 figures, 2 tables. $7.50.

Blood Clotting and Allied Problems. Transactions of the Fourth Conference January 22–23, 1951. *Edited by Joseph E. Flynn, Department of Pathology, College of Physicians and Surgeons, Columbia University.* New York, Josiah Macy, Jr., Foundation, 1951. 272 pages, 81 figures, 27 tables. $4.00.

The Prevention of Rheumatic Fever. *Lowell A. Rantz, M.D., Associate Professor of Medicine, Stanford University School of Medicine, San Francisco.* Springfield, Ill., Charles C Thomas, 1952. 66 pages, 1 figure, 5 tables. American Lectures in Circulation No. 125. $2.25.

L'Insuffisance Cardiaque Chronique Études Physiopathologiques. *Andre Cournand, Jean Lequime, and Paul Regniers, in collaboration with R. S. Cathcart, H. Denolin, M. I. Ferrer, R. M. Harvey, R. Pannier and D. W. Richards.* Paris, Masson et Cie, 1952. 262 pages, 51 tables, 21 figures.

La Malattia Sclerodermica. *Guido Bassi, with preface by Professor Giovannidi Guglielmo.* Bologan, Instituto Editoriale Medico, 1951, 710 pages, 185 figures.

Renal Function. Transactions of the Second Conference, October 19–20, 1950. *Edited by Stanley E. Bradley, Department of Medicine, College of Physicians and Surgeons, Columbia University.* New York, Josiah Macy, Jr. Foundation, 1951. 178 pages, 8 tables, 31 figures. $3.00.

Liver Injury. Transaction of the Ninth Conference, April 27–28, 1950. *Edited by F. W. Hoffbauer, M.D., Department of Medicine, University of Minnesota, Medical School, Minneapolis.* New York, Josiah Macy, Jr. Foundation, 1951. 232 pages, 101 figures, 12 tables. $3.00.

Adrenal Cortex. Transactions of Second Conference, Nov. 16–17, 1950. New York, Josiah Macy, Jr., Foundation, 1951. 209 pages, 68 figures, 15 tables. $3.00.

Conference on Problems of Aging. Transactions of Thirteenth Conference, Feb. 5–6 1951. *Edited by Nathan W. Shock, Chief, Section on Gerontology, National Heart Institute, National Institutes of Health and Baltimore City Hospitals.* New York, Josiah Macy, Jr. Foundation, 1951. 194 pages, 31 figures 9 tables. $4.00.

Factors Regulating Blood Pressure. Transactions of Fifth Conference, Feb. 15–16, 1951. *Edited by Benjamin W. Zweifach and Ephraim Shorr, Department of Medicine, Cornell University Medical College.* New York, Josiah Macy, Jr. Foundation, 1951. 238 pages, 49 figures, 25 tables. $3.75.

Nerve Impulse. Transactions of Second Conference, March 1–2, 1951. *Edited by David Nachmansohn, M.D. Department of Neurology, College of Physicians and Surgeons, Columbia University.* New York, Josiah Macy, Jr. Foundations, 1951. 204 pages, 37 figures, 4 tables. $3.50.

The Thoracic Surgical Patient—Preoperative, Anesthetic and Postoperative Care. *Lew A. Hochberg, M.D., with a foreword by Frank B. Berry, M.D.* New York, Grune & Stratton, Inc., 1952. 364 pages. $8.75.

Rheumatic Diseases Based on the Proceedings of the Seventh International Congress on Rheumatic Diseases. *Prepared by the Committee on Publications of the American Rheumatism Association. Chairman: Charles H. Slocumb, M.D.* Philadelphia, W. B. Saunders, 1952. 449 pages, 126 figures, 63 tables. $12.00.

The Clinical Use of Fluid and Electrolyte. *John H. Bland, M.D., Assistant Professor of Medicine, University of Vermont, College of Medicine.* Philadelphia, W. B. Saunders, 1952. 259 pages, 75 figures. $6.50.

Cardiac Emergencies and Heart Failure. Prevention and Treatment. *Arthur M. Master, M.D., Cardiologist, Mt. Sinai Hospital, New York, Marvin Mose, M.D., 1st Lt., USAF (MC) Walter Reed Army Hospital, Washington, D. C., Former Fellow in Cardiology, Mt. Sinai Hospital; and Harry Jaffe, M.D., Adjunct Physician, Cardiology, Mt. Sinai Hospital.* Philadelphia, Lea & Febiger, 1952. 159 pages, 13 figures, 4 tables. $3.00.

A Symposium on Essential Hypertension. An Epidemiologic Approach to the Elucidation of Its Natural History in Man. *The Committee on Symposium Program: Reginald H. Smithwick, M.D., E. Gurney Clark, M.D., and John A. Morsell, Ph.D.* Massachusetts, Commonwealth of Massachusetts, 1951. 373 pages, 66 figures, 22 tables, 11 charts.

Any Questions? A Selection of Questions and Answers. Published in the British Medical Journal. *Edited by Hugh Clegg, Editor of British Medical Journal.* 1951. (Agents. Grune & Stratton) 240 pages. $2.50.

Physical and Mental Stress and Consequential Development of Atherosclerosis. *Grethe Hartmann, and Fini Schulsinger.* Copenhagen, Rosenkilde and Bagger, 1952. 78 pages, 12 figures, 17 tables, 4 plates.

The Musculoskeletal System. A Symposium presented at the 23rd Graduate Fortnight of New York Academy of Medicine 1950. *Edited by Mahlon Ashford, M.D., New York Academy of Medicine.* New York, Macmillan, 1952. 368 pages, 103 figures, 15 tables. $6.50.

Differentialdiagnose Innerer Krankheiten. Eine Kurzgefasste Dorstellung fur Arzte und Studierende. *Dr. Robert Hegglin, Privatdozent an der Universitat Zurich.* Stuttgart, Georg Thieme, 1952. 454 pages, 220 figures, 8 tables. DM 49.80.

Die Krankhafte Blutdrucksteigerung. *Professor Dr. L. Hantschmann.* Stuttgart, Georg Thieme, 1952. 228 pages, 33 figures, 7 tables. DM 36.

Handbook of Cardiology for Nurses. The Disease, the Patient, Modern Concepts of Treatment. *Walter Modell, M.D., Assistant Professor, Cornell University, Medical College; Associate Cardiologist, Beth Israel Hospital and Hospital for Joint Diseases. Foreword by Edna L. Fritz, R. N. Assistant Professor of Medical Nursing, Cornell University, New York Hospital School of Nursing.* New York, Springer, 1952. 246 pages, 3 figures. $3.50.

Thoracic Aortography with Special Reference to its Value in Patent Ductus Arteriosus and Coarctation of the Aorta. *Gunnar Jonsson, Bror Broden and Johan Karnell.* Acta Radiologica Supplement #89, Stockholm, Sweden, 1951. 176 pages, 72 figures. Price, Sived. Cr. 30.

Progress in Allergy. *Edited by Paul Kallos, Helsingborg. Contributors: J. C. Ackroyd, London; R. Bircher, Basel; E. A. Brown, Boston; W. Hadorn, Bern; J. Harkavy, New York; D. Harley, London; L. Kallos, Deffner, Helsingborg; M. M. Peshkin, New York; E. Rothlin, Basel; A. H. Rowe, Oakland, California; A. Stoll, Basel; L. Unger, Chicago; F. Wyss, Bern.* Basel, S. Karger, 1952. 572 pages, 82 figures, one color plate and 61 tables. $16.50.

Le Depistage Radiologique Septematique des Affections du Thorax. Son Principe—Ses Modalites—Son Rendement. *Maurice Bariety, Professeur a la Faculté de Médecine de Paris, Médecin de l'Hotel-Dieu, and Charles Coury, Ancien Chef de Clinique a la Faculté de Médecine, Médecin Assis-*

'ant Deo Hopitaux de Paris. Masson et Cie, Paris, 1952. 216 pages, 58 tables and 10 graphs. 1800 francs.

Syphilis et Lesions Cardio-vasculaires. *R. Lutembacher.* Masson et Cie, Paris, 1951. 224 pages, 11 figures. 2300 fr.

Control High Blood Pressure and Live Longer. *Herman Pomeranz, Visiting Physician, Manhattan General Hospital, New York.* New York, Avon, 1952. 239 pages. $.35.

Medizinische Rontgentechnik. Lehrbuch fur Medizinisch-Technische Assistentinnen, Studierende und Arzti. Volume II. Physikalisch-Technischer. I. Grundlagen der Strahlendiagnostik und Strahlentherapie, Apparatckunde. II. Röntgen-und Farben Photographie. *Edited by Prof. Dr. Herbert Schoen. Part II by Dipl.-Physiker Erich Bunde, Karlsruhe and Dr. Viktor Loeck, Wuppertal-Elberfeld.* Stuttgart, Georg Thieme 1952. 360 pages, 217 figures. Price, Ganzleinen DM 27.

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N. Y.

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NEW FEATURE

Beginning with the January 1, 1953 issue, Circulation will carry a Section on Conferences, to be edited by Edgar V. Allen, M.D., and J. Earle Estes, M.D. The new section will be published six times annually and will cover clinical and clinicopathologic conferences on specific subjects.

Experts will cover each field of cardiac and circulatory diseases, using the question and answer method wherever possible.

NEW CHAIRMAN

Dr. J. Scott Butterworth, Associate Professor of Medicine at New York University Postgraduate Medical School, has been appointed Chairman of the Educational Committee of the American Heart Association's Scientific Council.

WEST COAST SYMPOSIA

The Los Angeles County Heart Association will sponsor Symposia on Pharmacology of Cardiovascular Diseases, on Hypertension and on Peripheral Vascular Diseases, on October 15 and 16 at the Wilshire-Ebell Theatre in Los Angeles.

The six guest speakers will be C. Sidney Burwell, M.D., of the Harvard Medical School; Julius H. Comroe, Jr., M.D., of the University of Pennsylvania; Keith S. Grimson, M.D., of Duke University; Robert L. King, M.D., University of Washington School of Medicine and President-Elect of the American Heart Association; and Maurice L. Tainter, M.D., former professor of Pharmacology at Stanford University.

GRANTS-IN-AID APPLICATIONS

Applications for research grants-in-aid for the fiscal year 1953–54 should be forwarded to the Medical Director of the American Heart Association, postmarked not later than December 1, 1952.

ANNUAL MEETING AND SCIENTIFIC SESSIONS

The Twenty-Ninth Annual Meeting and the Twenty-Sixth Scientific Sessions of the American Heart Association will be held at the *Hotel Chelsea* in Atlantic City, N. J., *April 8–12, 1953*, immediately preceding the annual meeting of the American College of Physicians. All those desiring to attend should make room reservations at the earliest possible date. (The Hotel Chelsea is located on the Boardwalk at Morris Avenue, five blocks *south* of the Convention Hall.) The Scientific Sessions will be held on Thursday, Friday, Saturday and Sunday, April 9, 10, 11 and 12.

PAPERS FOR THE SCIENTIFIC SESSIONS

All those desiring to present papers at the Association's Scientific Sessions should submit abstracts *in triplicate* of the proposed presentation to Dr. André Cournand, Chairman of the Program Committee, c/o American Heart Association, 44 East 23rd Street, New York 10, N. Y., not later than *January 1, 1953*. Abstracts should not be longer than 300 words and must contain in summary form, a specific statement of the results obtained or conclusions reached (not merely a statement that results or conclusions will be presented, or discussed at the meeting.)

COURSE ON CONGENITAL HEART DISEASE

A three day postgraduate course on congenital heart disease will be held under the auspices of the Medical School of the University of Utah on November 19, 20, and 21, as a preliminary to the regional meeting of the American College of Chest Physicians. Visiting faculty for the course will include Dr. Lewis Dexter, Assistant Professor in the Department of Medicine at Harvard University; Dr. Jesse Edwards, Assistant Professor in the Department of Pathology and Anatomy at the Mayo Clinic in Rochester, Minnesota; and Dr. Marcy Sussman, specialist in Radiology, of Phoenix, Arizona.

The registration fee for this course will be $30.00. A fee of $5.00 should accompany the application for this course, which is applicable to the total registration fee.

Address all inquiries to the Director, Division of Graduate and Postgraduate Medical Education, 175 East 21st Street, Salt Lake City, Utah.

WASHINGTON STATE SYMPOSIUM

The Washington State Heart Association in cooperation with the Washington State Department of Health will present their Fourth Annual Symposium on "Hypertension" and "The Arrhythmias" on November 7 and 8 at the University of Washington Medical School Auditorium. Speakers will include Drs. Robert W. Wilkins, Boston; Stanley E. Bradley, New York; Eugene B. Ferris, Cincinnati; and Myron Prinzmetal, Los Angeles.

CALENDAR

Oct. 3–4: European Society of Cardiovascular Surgery, Strasbourg, France. Sir James Learmonth, Dept. of Surgery, University New Buildings, Edinburgh 8, Scotland.

Oct. 12–16: World Medical Association, Athens, Greece. Dr. Louis H. Bauer, Secretary-General, 2 East 103rd Street, New York 29, N. Y.

Oct. 16–18: World Congress of Medicine, Montecatini, Italy. Secretariat: Corso Trieste, 65, Rome, Italy.

Oct. 20–24: 80th Annual Meeting, American Public Health Association, Cleveland, Ohio. Reginald M. Atwater, M.D., Executive Secretary, 1790 Broadway, New York 19, N. Y.

Nov. 6: Fall meeting of the Midwest Section of the American Federation for Clinical Research, Congress Hotel, Chicago, Ill. Robert L. Grissom, M.D., Secretary.

Nov. 10–12: Association of American Medical Colleges, 63rd Annual Meeting, Hotel Broadmoor, Colorado Springs, Colo. Dean F. Smiley, M.D., Secretary, 185 North Wabash Avenue, Chicago 1, Ill.